Modeling Red Blood Cell and Iron Dynamics in Patients Undergoing Periodic EPO and Iron Treatments

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February 4, 2013

Abstract

Chronic kidney disease causes a slow loss of kidney function over time and can eventually lead to End Stage Renal Disease, where a patient must undergo dialysis to remove fluids and wastes from the body. These patients also suffer from a lack of the hormone erythropoietin (EPO), produced in the kidneys, that stimulates red blood cell (RBC) production. Without intervention, patients suffer from anemia. Patients are treated with both EPO and iron in order to stimulate RBC production.

We develop a partial differential equation model for RBC dynamics using two structure variables, one for age and one for cellular iron endowment. We couple this with a set of ordinary differential equations modeling iron dynamics. We take into account the effects of both inflammation and neocytolysis, which are known to affect patients undergoing treatment.

A detailed description of our numerical methods is given, and some simulation results are presented.

Keywords: mathematical model, mathematical biology, erythropoiesis, erythrocyte, red blood cell, chronic kidney disease, dialysis, iron, neocytolysis, hepcidin, EPO, hemoglobin

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1 Introduction

It is estimated that 31 million Americans have chronic kidney disease (CKD). Among those, approximately 330 thousand were classified as being in End-Stage Renal Disease (ESRD) and required dialysis [43] to remove wastes and fluids from the blood. For the purposes of this study, we consider only hemodialysis, where a patient's blood is exposed to a semipermeable membrane outside of the body.

In addition to regulating blood pressure and filtering waste products from blood, kidneys produce a hormone called erythropoietin (EPO) that is the major regulator of erythropoiesis, or red blood cell production. EPO level is normally controlled by a negative feedback mechanism in the kidneys, but patients in ESRD do not produce sufficient levels of EPO to maintain blood hemoglobin concentration. Hemoglobin is the protein that gives red blood cells the ability to carry oxygen. Patients with low hemoglobin concentration may present symptoms of anemia, such as decreased cardiac function, fatigue, and decreased cognitive function.

In order to prevent anemia, patients typically receive recombinant human EPO (rHuEPO) intravenously to stimulate red blood cell production. However, treatment is far from perfect. In 2006, only half of dialysis patients had a mean monthly hemoglobin greater than 11 grams per deciliter [43], the desired minimum level set by the National Kidney Foundation [30].

Iron is required to produce hemoglobin, and iron deficiency can be an issue among patients receiving rHuEPO therapy. Oral iron supplementation is often ineffective, so intravenous iron supplementation has become a mainstay in many patients undergoing rHuEPO therapy [26].

Iron availability is negatively affected by inflammation level in the body. Most patients with CKD have elevated levels of inflammation due to CKD and the presence of other medical issues (e.g., diabetes, hypertension, etc.) [27].

We develop a model for red blood cell populations using two structure variables, one for age-structuring and one to account for a cellular iron endowment. We couple these partial differential equations with a system of ordinary differential equations that models the iron cycle, and then describe how to solve the complete system of differential equations numerically. We then present some of our simulated results, and comment on the qualitative behavior of the model in various prescribed situations.

2 Previous models

The process of erythropoiesis has been modeled in several physiological scenarios. In [32], rHuEPO therapy is considered in healthy individuals. This model incorporates the negative feedback to endogenous EPO production. EPO is assumed to be cleared using Michaelis-Menten dynamics. A similar model was used to fit data in rats [47]. Both of these models use delay instead of age-structured modeling.

Both [7] and [8] use age-structured models, as does the model described in [28], which assumes that the oldest mature erythrocytes will be destroyed, yielding a moving boundary condition. In [2], EPO is assumed to accelerate maturation of cells undergoing erythropoiesis. Additionally, EPO is assumed to be consumed during the process of erythropoiesis.

The model presented here is a significant departure from these models in that it incorporates iron. Additionally, we have accounted for the effects of inflammation and neocytolysis, which is a down-regulating mechanism by which red blood cells are selectively destroyed when blood oxygen level rises.

The authors have previously presented a more simplified version of this model in [5, 9], including

simulations. The simplified model is significantly less sophisticated, as assumptions were made there so that simulations would be more tractable. It should also be mentioned that an earlier iteration of the current model was presented by the authors in [6]; the model presented here incorporates several corrections (to errata in formulae, parameter constraints, and figures) and improvements (e.g., new representations of certain boundary conditions), but is otherwise essentially identical to that earlier model iteration. The numerical procedures and simulation results presented here, however, are completely new.

3 Overview of Red Blood Cell Production

Erythrocytes are produced primarily from stem cells in bone marrow. In the presence of certain hormones, stem cells divide asymmetrically, producing a committed colony-forming-unit (CFU) while maintaining the population of stem cells. Erythrocyte lineage continues as depicted in Figure 1: erythroid burst-forming unit (BFU-E), erythroid colony-forming-unit (CFU-E), proerythrocyte, basophilic erythrocyte, polychromatic erythroblast, orthochromatic erythroblast, reticulocyte, and erythrocyte.

Hemoglobin is synthesized beginning in the basophilic erythrocyte stage, with the majority of synthesis occurring in the polychromatic erythroblast stage. When the nucleus is extruded from the cell, the cell is named a reticulocyte. Little hemoglobin synthesis happens at the reticulocyte stage, and synthesis is completely absent in mature erythrocytes [21]. Reticulocytes begin to lose the adhesive proteins that hold them in the bone marrow. They decrease in size and begin to circulate in the blood. In healthy individuals, erythrocyte life span is approximately 120 days, at which time aging erythrocytes are enveloped by macrophages in the spleen.

In a healthy individual, an increase in blood oxygen level is detected by the kidneys, which in turn

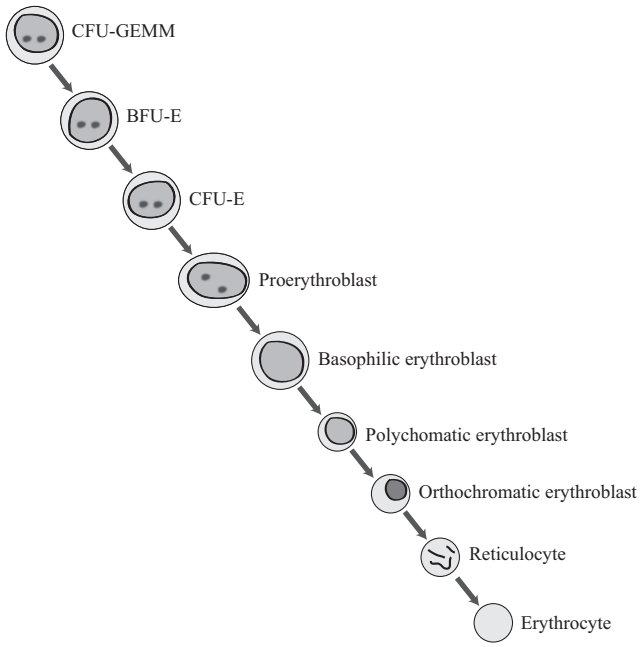


Figure 1: Erythropoiesis cell lineage.

decrease production of EPO. Down-regulation of the RBC production is achieved by the increased death rate of RBC progenitors due to this decrease in EPO. However, it takes 18 to 21 days for cells to mature and be released into circulation, so this down-regulation has a long delay before it actually affects blood oxygen level. Additionally, down-regulation would only cause the circulating red cell mass to drop by about 1% per day [33].

Neocytolysis has been observed in astronauts entering space [4, 44] and in high altitude dwellers who descend to sea level [29, 35]; all have higher aggregate RBC mass than needed. Their RBC mass was decreased by 10-15% in a few days, which could not be explained by simple down-regulation of RBC production.

Neocytolysis, believed to be caused by a drop in EPO level, is a physiological process that aids in this control of the red cell mass by causing the selective destruction of young circulating RBCs [12, 33]. Since these cells were circulating and contributing to blood oxygen level, their death has a much faster effect on blood oxygen level than the down-regulation of the production cycle. Neocytolysis has been determined to contribute to the anemia of renal disease [3, 34], as patients undergoing therapy have constantly fluctuating EPO levels.

4 RBC Model

Cells in the RBC lineage divide, differentiate, and die under the influence of several environmental factors. Figure 2, a modification of a figure in [23], illustrates various aspects of the system we will model, and indicates which cells in the RBC lineage are affected in each case. In particular, this figure suggests five cell classes, or compartments, that one might consider in formulating a mathematical model to describe the behavior of these cells:

- P_1: early BFU-E
- P_2: late BFU-E, CFU-E, proerythroblasts, and early basophilic erythroblasts
- P_3: late basophilic erythroblasts and early polychromatic erythroblasts
- P_4: late polychromatic erythroblasts, orthochromatic erythroblasts, and non-circulating reticulocytes
- P_5: mature erythrocytes and circulating reticulocytes.

We discuss each of these compartments individually in Sections 4.2 through 4.6. The stages in the erythroid cell progression that biologists have chosen to name (see Figure 1) are based on distinguishing characteristics observed when these cells are collected, stained, and viewed through a microscope. It is not surprising that we choose our five classes of cells differently as we focus on cell interactions with EPO and iron and the location of the cells (in the bone marrow or circulating). The current RBC lineage model is represented in Figure 3. We introduce the model for the iron compartments in Section 5.

4.1 Derivation of Model Equations

We propose a model for cell populations that depends on structure variables representing maturity level and cellular iron level. The structure variable μ_i denotes the maturity level for cells in class P_i and γ denotes the iron level (when appropriate). Thus, $P_3(t, \mu_3, \gamma)$ is the *density* of cells (in billions per maturity level per iron level) in class P_3 at time t, maturity level μ_3, and iron state γ. If we imagine μ_i and γ to be *spatial* variables, then $P_i(t, \mu_i, \gamma)$ may be properly described as a density

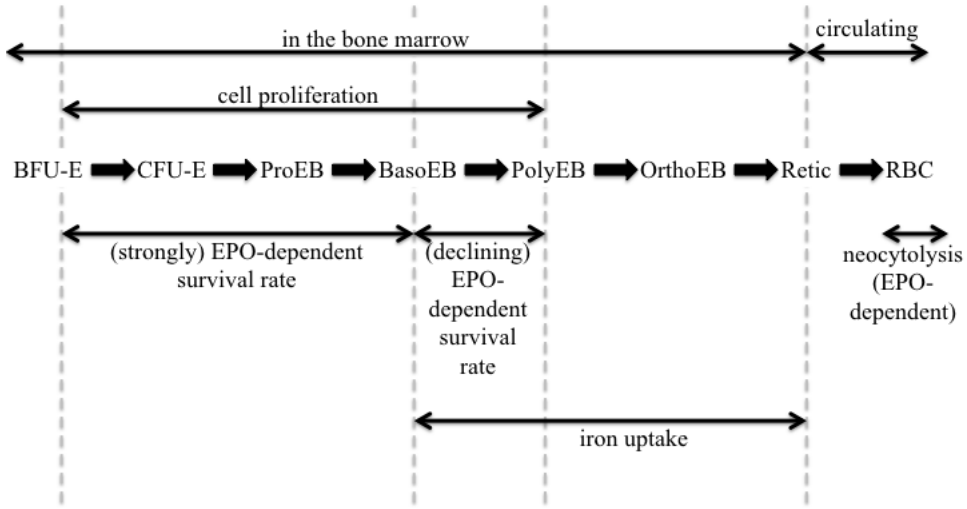


Figure 2: Stages of red blood cell production. We use the following short-hand notations: BFU-E = burst-forming unit–erythroid, CFU-E = colony-forming unit–erythroid, ProEB = proerythroblast, BasoEB = basophilic erythroblast, PolyEB = polychromatic erythroblast, OrthoEB = orthochromatic erythroblast, Retic = reticulocyte, RBC = red blood cell.

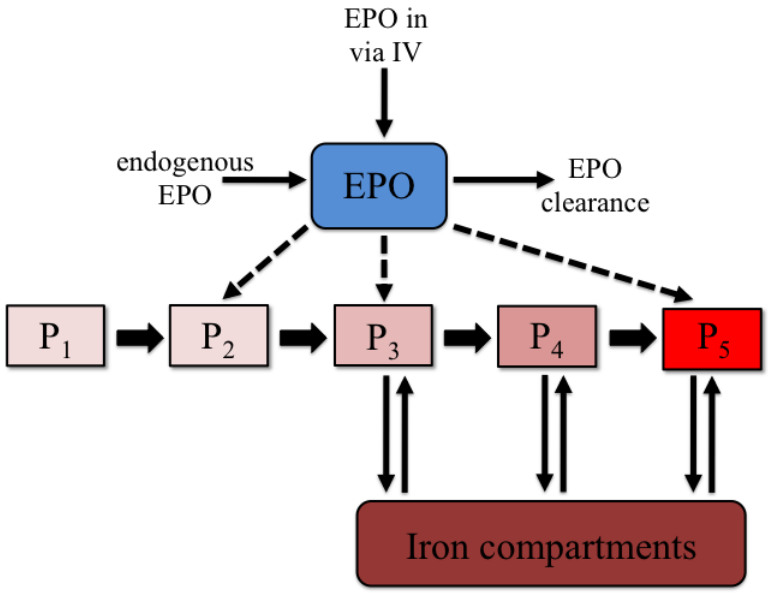


Figure 3: Model schematic. Note that the states variables are $P_1(t, \mu_1)$, $P_2(t, \mu_2)$, $P_3(t, \mu_3, \gamma)$, $P_4(t, \mu_4, \gamma)$, $P_5(t, \mu_5, \gamma)$ and $EPO(t)$. The iron model is described in Section 5.

in billions of cells per unit *area* for $i \in \{3, 4, 5\}$. The situation for classes P_1 and P_2 is slightly different because cells in these classes have no iron; therefore, $P_i(t, \mu_i)$ may be described as a density in billions of cells per maturity level (or, per unit *length*) for $i \in \{1, 2\}$. Each class is assumed to have a maximum maturity level given by $(\mu_i)_f$.

Throughout the following discussion, β will indicate a birth/proliferation rate, δ will indicate a death rate, and ρ will indicate other rates (maturation rates, rates of treatment, etc.).

We begin by deriving the model equations that describe the behavior of cells in classes P_3 through P_5. We will assume that the iron state structure variable γ varies from 0 to $\gamma_f = 2$, where $\gamma_{full} = \frac{\gamma_f}{2} = 1$ represents the amount of iron (in mg) that the "typical" RBC contains in a healthy individual. We also assume that when a cell divides, each daughter cell inherits half of the parent cell's iron. Therefore, when a cell with iron state γ divides, it leaves iron state γ and two cells enter iron state $\frac{\gamma}{2}$. Similarly, for each cell in iron state 2γ that divides, two cells enter iron state γ.

We derive equations for those classes that incorporate iron (i.e., classes P_3, P_4, and P_5) by considering an arbitrary $\Delta\mu \times \Delta\gamma$ region at some time t. This region lies in the plane representing possible values of the *spatial* variables and contains the point (μ, γ), and we assume at first that $0 \le \gamma \le \frac{\gamma_f}{2} = 1$. Such a region is depicted in Figure 4. To develop our model, we consider the time rate of change of the cell population in this arbitrary region. This is given by

$$\frac{\partial}{\partial t} \int_{\gamma}^{\gamma+\Delta\gamma} \int_{\mu}^{\mu+\Delta\mu} P(t, \xi, \zeta) d\xi d\zeta$$

$$\begin{aligned}
&= 2[\text{birth rate of cells with twice the iron level as cells inside this region}] \\
&\quad - [\text{birth rate of cells inside this region}] - [\text{death rate of cells inside this region}] \\
&\quad + [\text{rate of maturation of cells at maturity } \mu] \\
&\quad - [\text{rate of maturation of cells at maturity } \mu + \Delta\mu] \\
&\quad + [\text{rate of hemoglobinization of cells at iron state } \gamma] \\
&\quad - [\text{rate of hemoglobinization of cells at iron state } \gamma + \Delta\gamma]
\end{aligned}$$

$$\begin{aligned}
&= 2 \int_{\gamma}^{\gamma+\Delta\gamma} \int_{\mu}^{\mu+\Delta\mu} \beta P(t, \xi, 2\zeta)\, d\xi\, d\zeta - \int_{\gamma}^{\gamma+\Delta\gamma} \int_{\mu}^{\mu+\Delta\mu} \beta P(t, \xi, \zeta)\, d\xi\, d\zeta \\
&\quad - \int_{\gamma}^{\gamma+\Delta\gamma} \int_{\mu}^{\mu+\Delta\mu} \delta P(t, \xi, \zeta)\, d\xi\, d\zeta + \int_{\gamma}^{\gamma+\Delta\gamma} \rho P(t, \mu, \zeta)\, d\zeta - \int_{\gamma}^{\gamma+\Delta\gamma} \rho P(t, \mu + \Delta\mu, \zeta) d\zeta \\
&\quad + \int_{\mu}^{\mu+\Delta\mu} h P(t, \xi, \gamma) d\xi - \int_{\mu}^{\mu+\Delta\mu} h P(t, \xi, \gamma + \Delta\gamma) d\xi,
\end{aligned}$$

where β is the proliferation rate, δ is the death rate, ρ is the maturation rate, and h is the hemoglobinization rate (equivalent to the rate of iron uptake), which generally depends on the plasma iron level Fe_{pl} (described later).

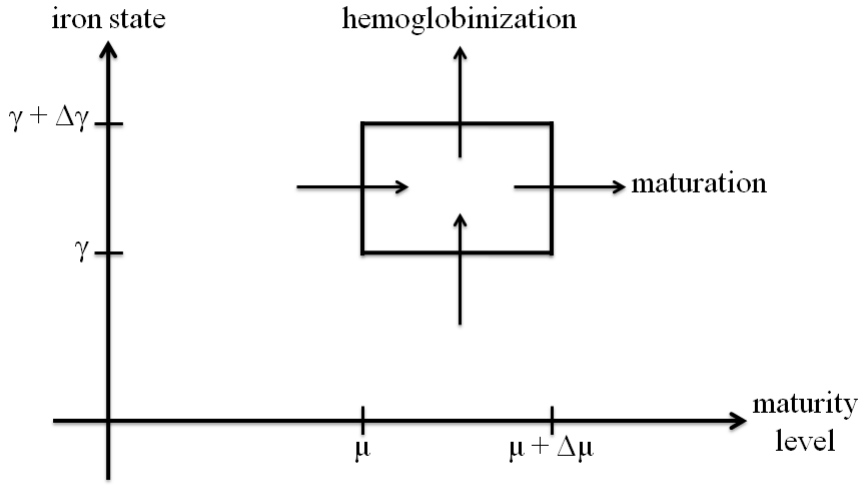


Figure 4: Arbitrary infinitesimal region for classes that incorporate iron.

We rearrange these to obtain

$$\begin{aligned}\frac{\partial}{\partial t}\int_{\gamma}^{\gamma+\Delta\gamma}\int_{\mu}^{\mu+\Delta\mu} P(t,\xi,\zeta)\,d\xi\,d\zeta = 2\int_{\gamma}^{\gamma+\Delta\gamma}\int_{\mu}^{\mu+\Delta\mu}\beta P(t,\xi,2\zeta)\,d\xi\,d\zeta \\ -\int_{\gamma}^{\gamma+\Delta\gamma}\int_{\mu}^{\mu+\Delta\mu}[\beta+\delta]P(t,\xi,\zeta)\,d\xi\,d\zeta \\ -\int_{\gamma}^{\gamma+\Delta\gamma}\rho\left[P(t,\mu+\Delta\mu,\zeta)-P(t,\mu,\zeta)\right]\,d\zeta \\ -\int_{\mu}^{\mu+\Delta\mu}h\left[P(t,\xi,\gamma+\Delta\gamma)-P(t,\xi,\gamma)\right]\,d\xi,\end{aligned}$$

then divide by $\Delta\mu\Delta\gamma$ to arrive at

$$\begin{aligned}\frac{\partial}{\partial t}\left[\frac{1}{\Delta\gamma}\int_{\gamma}^{\gamma+\Delta\gamma}\frac{1}{\Delta\mu}\int_{\mu}^{\mu+\Delta\mu} P(t,\xi,\zeta)\,d\xi\,d\zeta\right] = \frac{2}{\Delta\gamma}\int_{\gamma}^{\gamma+\Delta\gamma}\frac{1}{\Delta\mu}\int_{\mu}^{\mu+\Delta\mu}\beta P(t,\xi,2\zeta)\,d\xi\,d\zeta \\ -\frac{1}{\Delta\gamma}\int_{\gamma}^{\gamma+\Delta\gamma}\frac{1}{\Delta\mu}\int_{\mu}^{\mu+\Delta\mu}[\beta+\delta]P(t,\xi,\zeta)\,d\xi\,d\zeta \\ -\frac{1}{\Delta\gamma}\int_{\gamma}^{\gamma+\Delta\gamma}\rho\frac{P(t,\mu+\Delta\mu,\zeta)-P(t,\mu,\zeta)}{\Delta\mu}\,d\zeta \\ -\frac{1}{\Delta\mu}\int_{\mu}^{\mu+\Delta\mu}h\frac{P(t,\xi,\gamma+\Delta\gamma)-P(t,\xi,\gamma)}{\Delta\gamma}\,d\xi.\end{aligned}$$

Taking the limit as $\Delta\mu\to 0$ and $\Delta\gamma\to 0$, we obtain

$$\frac{\partial}{\partial t}P(t,\mu,\gamma) = 2\beta P(t,\mu,2\gamma) - [\beta+\delta]P(t,\mu,\gamma) - \frac{\partial}{\partial\mu}\rho P(t,\mu,\gamma) - \frac{\partial}{\partial\gamma}hP(t,\mu,\gamma)$$

as the general form for the equations governing cells in classes P_3 through P_5 for the case in which $0 \leq \gamma \leq \frac{\gamma_f}{2}$. Note that the rates β, δ, ρ and h could be functions that depend on μ, γ, or other states in the system.

By our assumptions, the maximum iron state is γ_f, so cell division cannot yield a cell with iron state $\gamma > \frac{\gamma_f}{2}$. Thus, for cells with iron states greater than $\frac{\gamma_f}{2}$, we omit the birth rate term associated with iron state 2γ to obtain the equation

$$\frac{\partial}{\partial t}P(t,\mu,\gamma) = -[\beta+\delta]P(t,\mu,\gamma) - \frac{\partial}{\partial \mu}\rho P(t,\mu,\gamma) - \frac{\partial}{\partial \gamma}hP(t,\mu,\gamma).$$

Our generic balance laws for classes P_3 through P_5 can therefore be written as

$$\begin{aligned}\frac{\partial}{\partial t}P(t,\mu,\gamma) = \chi_{[0,\frac{\gamma_f}{2}]}(\gamma)2\beta P(t,\mu,2\gamma) - [\beta+\delta]P(t,\mu,\gamma) - \frac{\partial}{\partial \mu}\rho P(t,\mu,\gamma) \\ - \frac{\partial}{\partial \gamma}hP(t,\mu,\gamma),\end{aligned} \tag{1}$$

where $\chi_{[0,\frac{\gamma_f}{2}]}$ is the characteristic function given by

$$\chi_{[0,\frac{\gamma_f}{2}]}(\gamma) = \begin{cases} 1 & \text{for } \gamma \in [0,\frac{\gamma_f}{2}] \\ 0 & \text{otherwise.} \end{cases}$$

Cells in classes P_1 and P_2 do not incorporate iron, so the densities $P_1(t,\mu_1)$ and $P_2(t,\mu_2)$ are functions of only time and maturity level. The general form of the partial differential equations governing these classes, derived in [5], is

$$\frac{\partial}{\partial t}P(t,\mu) = [\beta-\delta]P(t,\mu) - \frac{\partial}{\partial \mu}\rho P(t,\mu), \tag{2}$$

where β is the proliferation rate, δ is the death rate, and ρ is the maturation rate. It should be noted that $P_1(t,\mu_1)$ and $P_2(t,\mu_2)$ have units of billions of cells per maturity level. That is, units for these two classes differ from the units used for the the three classes described above.

4.2 Class P_1

Class P_1 consists of early BFU-E. These are the most immature cells that are committed to the erythroid lineage. We make the following assumptions about cells in this class.

1. The maturation rate ρ_1 is constant.
2. BFU-E differentiate into CFU-E in approximately seven days [36, 39]. BFU-E begin expressing EPO receptors (EPORs), which means that, in time, they do become influenced by EPO. Hence, we allow for cells to reside in class P_1 for three days (during which they are not influenced by EPO), while late BFU-E are in class P_2 (where they are influenced by EPO). Therefore we choose the maximum maturity level to be $(\mu_1)_f = 3$.
3. The majority of cell proliferation happens in later classes [23, 24], so we set birth rate equal to death rate for cells in this class.

Hence, for class P_1, equation (2) becomes

$$\frac{\partial}{\partial t}P_1(t,\mu_1) = -\rho_1 \frac{\partial}{\partial \mu_1}P_1(t,\mu_1) \tag{3}$$

with initial condition

$$P_1(0,\mu_1) = P_1^{init}(\mu_1)$$

and boundary condition at $\mu_1 = 0$

$$P_1(t,0) = P_1^{bdy}(t).$$

4.3 Class P_2

Class P_2 consists of late BFU-E, CFU-E, proerythroblasts, and early basophilic erythroblasts. We make the following assumptions about cells in class P_2.

1. The maturation rate ρ_2 is constant.
2. Cells reside in this class for twelve days [18, 36], and therefore $(\mu_2)_f = 12$.
3. During the time cells reside in class P_2, they undergo approximately 6 cell divisions [18, 19, 20, 23]. We therefore assume a constant birth rate of $\beta_2 = \frac{\ln(2^6)}{12}$ days^{-1}.
4. Cells in this class express EPORs [24, 38], and this interaction of EPO with EPOR is the most important control point for erythropoiesis [18, 37, 48]. Cells at this stage depend absolutely on EPO for their survival and will undergo apoptosis in its absence [24, 39]. Even in healthy individuals, complete survival of progenitors would require an EPO level much higher than normal level; the normal production rate of RBCs represents survival of only a minority of progenitor cells [23]. Therefore we choose the death rate to be a decreasing function of the EPO level:

$$\delta_2(EPO) = \left(\delta_2^{max} - \delta_2^{min}\right) \cdot \frac{\left(c_{\delta_2}\right)^{k_{\delta_2}}}{\left(c_{\delta_2}\right)^{k_{\delta_2}} + \left(EPO\right)^{k_{\delta_2}}} + \delta_2^{min}.$$

Thus, using equation (2), the state equation for class P_2 becomes

$$\frac{\partial}{\partial t}P_2(t,\mu_2) = [\beta_2 - \delta_2(EPO)]P_2(t,\mu_2) - \rho_2 \frac{\partial}{\partial \mu_2}P_2(t,\mu_2), \tag{4}$$

with initial condition

$$P_2(0,\mu_2) = P_2^{init}(\mu_2)$$

and boundary condition at $\mu_2 = 0$

$$P_2(t,0) = P_2^{bdy}(t) = P_1(t,(\mu_1)_f).$$

4.4 Class P_3

Class P_3 consists of late basophilic erythroblasts and early polychromatic erythroblasts. We make the following assumptions about cells in class P_3.

1. The maturation rate ρ_3 is constant.

2. Cells reside in this class for 1 day [18, 36], and therefore $(\mu_3)_f = 1$.

3. Cells in this stage continue to proliferate [18]. We therefore assume a constant birth rate of $\beta_3 = \ln(2)$ days^{-1}, which corresponds to one cell division per day.

4. Cells in class P_3 continue to express EPORs, but the level of expression declines significantly as cells mature through this class [13]. Hence, cells in this class become less dependent on EPO for survival. We model this as

$$\delta_3(\mu_3, EPO) = \delta_3^{max}(\mu_3) \cdot \frac{\left(c_{\delta_3}\right)^{k_{\delta_3}}}{\left(c_{\delta_3}\right)^{k_{\delta_3}} + \left(EPO\right)^{k_{\delta_3}}}$$

   where δ_3^{max} is a decreasing function of μ_3. For our model, we assume δ_3^{max} to be an affine function given by

$$\delta_3^{max}(\mu_3) = -m_3\mu_3 + b_3,$$

   where $m_3 > 0$ and $b_3 - m_3 \cdot (\mu_3)_f > 0$. For a fixed maturity level μ_3, δ_3 is a decreasing sigmoid function of EPO. That is, at a fixed maturity level, as EPO increases, the death rate decreases. If we consider instead a fixed EPO level, then increasing maturity level causes a decrease in the maximum death rate. That is, low EPO affects younger cells in this class more than it affects more mature cells. Both the fixed maturity level and fixed EPO level phenomena are depicted in Figure 5.

5. Cells in class P_3 express transferrin receptors (Tfr) and begin the process of taking in iron and synthesizing hemoglobin [18, 23]. The rate of hemoglobinization (or equivalently, iron uptake) is a function of iron level Fe_{pl} (in the blood plasma) and iron state γ (of a cell). Complete descriptions of the hemoglobinization rate, $h_3(Fe_{pl}, \gamma)$, and the state variable Fe_{pl} appear in Sections 4.7 and 5.4.

Hence, for class P_3, equation (1) becomes

$$\frac{\partial}{\partial t}P_3(t, \mu_3, \gamma) = \chi_{[0, \frac{\gamma_f}{2}]}(\gamma) 2\beta_3 P_3(t, \mu_3, 2\gamma) - [\beta_3 + \delta_3(\mu_3, EPO)]P_3(t, \mu_3, \gamma) - \rho_3 \frac{\partial}{\partial \mu_3}P_3(t, \mu_3, \gamma) - \frac{\partial}{\partial \gamma}\Big[h_3(Fe_{pl}, \gamma)P_3(t, \mu_3, \gamma)\Big]. \quad (5)$$

The initial condition for these cells can be given by

$$P_3(0, \mu, \gamma) = P_3^{init}(\mu, \gamma)$$

for $(\mu, \gamma) \in (0, (\mu_3)_f] \times [0, \gamma_f]$. There are also two boundary conditions as described below.

The $\gamma = 0$ boundary condition is given by

$$h_3(Fe_{pl}, 0)P_3(t, \mu_3, 0) = 0 \quad (6)$$

for $\mu_3 \in [0, (\mu_3)_f]$. Cells clearly cannot have a negative iron level, so this boundary condition ensures that there is no movement of cells across the boundary separating the regions of negative and non-negative iron states. Based on this description, the foregoing boundary condition may be regarded as a "zero-flux" boundary condition, although the terms involved do not lead to typical units of flux.

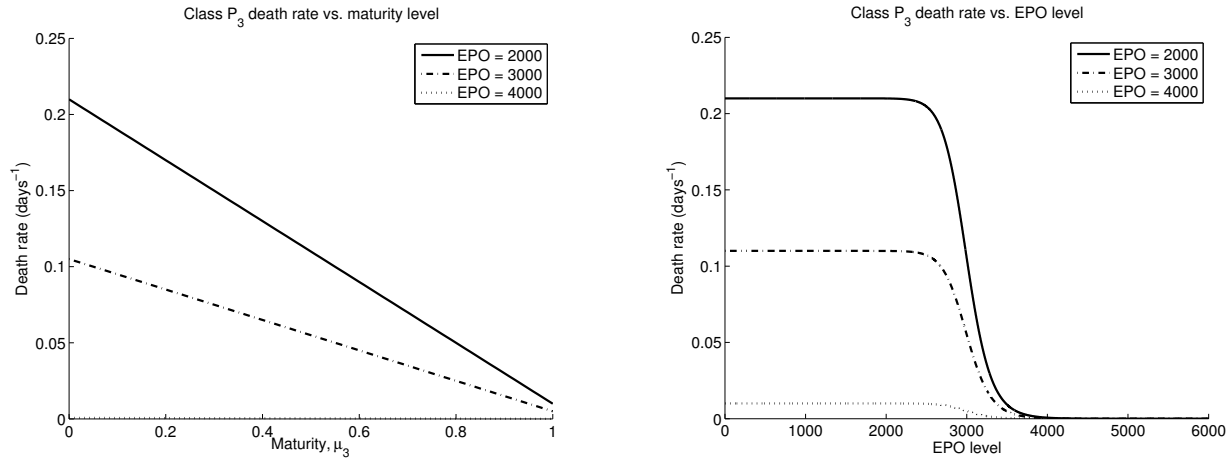


Figure 5: Death rate in class P_3 is a function of both maturity level, μ_3, and EPO level. For a fixed EPO level, death rate decreases as maturity level increases. For a fixed maturity level, death rate is larger when EPO is small. These plots were generated with parameter values $m_3 = 0.2$, $b_3 = 0.21$, $c_{\delta_3} = 3000$ and $k_{\delta_3} = 20$.

The $\mu_3 = 0$ boundary condition is given by

$$P_3(t, 0, \gamma) = P_3^{bdy,\mu}(t, \gamma) = P_2(t, (\mu_2)_f)p(\gamma), \tag{7}$$

where p is a probability density function with support on some subset of $[0, \gamma_f]$ (i.e., a function satisfying $p(x) \geq 0$ for all x and $\int_0^{\gamma_f} p(x)\,dx = 1$.) This condition ensures that the number of cells per maturity level entering class P_3 matches the number of cells per maturity level leaving class P_2 since

$$\int_0^{\gamma_f} P_3(t, 0, \gamma)\,d\gamma = \int_0^{\gamma_f} P_2(t, (\mu_2)_f)p(\gamma)\,d\gamma = P_2(t, (\mu_2)_f)\int_0^{\gamma_f} p(\gamma)d\gamma = P_2(t, (\mu_2)_f).$$

From a biological perspective, the most reasonable choice for p is a Dirac delta function with support at $\gamma = 0$. This would ensure that all cells entering class P_3 from class P_2 have zero iron. Unfortunately, this choice for p does not bode well for numerical solution of the above-described initial/boundary value problem, so we consider instead beta probability density functions. That is, we choose p to have the form

$$p(\gamma) = \begin{cases} \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}\gamma^{a-1}(1-\gamma)^{b-1} & \text{for } \gamma \in [0,1] \\ 0 & \text{otherwise,} \end{cases} \tag{8}$$

where a and b are parameters that define specific beta distribution. One possibility would be to use the beta distribution with parameters $a = 2$ and $b = 20$ as shown in Figure 6. Note that boundary condition (7) with this choice of p ensures that all of the cells transitioning from class P_2 into class P_3 are conserved, but defies our physical intuition that all cells entering P_3 from P_2 should start out with iron level 0. Technically, the iron required to distribute the class P_3 cells along the $\mu = 0$ boundary should be subtracted from the iron in the blood plasma, Fe_{pl}, to avoid net growth of iron in the system, but we assume that the amount of iron added to the system is neglible if the beta distribution parameters a and b are chosen appropriately.

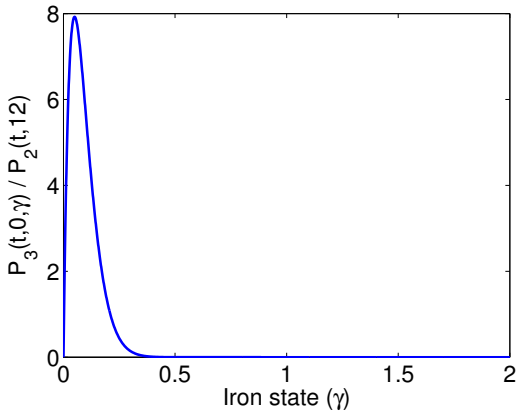


Figure 6: Plot of a beta distribution with parameters $a = 2$ and $b = 20$. This distribution can be used to express the $\mu = 0$ boundary conditions for class P_3.

4.5 Class P_4

Class P_4 contains late polychromatic erythroblasts, orthochromatic erythroblasts, and non-circulating reticulocytes, which are the last stages of erythroid cells residing in the bone marrow. We make the following assumptions about cells in class P_4.

1. The maturation rate ρ_4 is constant.
2. Cells reside in this class for 2 days [18, 36], and therefore $(\mu_4)_f = 2$.
3. Cells in this class have stopped proliferating [18, 23]. Thus, $\beta_4 = 0$.
4. It is well-documented that red blood cells have a shorter life span in individuals with iron deficiency [11, 14, 15, 45]. Hence, we assume that any RBCs in class P_4 that are severely iron deficient have increased mortality.

   We begin by defining c_{δ_4} as an increasing function of μ_4. For simplicity, we choose an affine function of the form

   $$c_{\delta_4}(\mu_4) = m_4\mu_4 + b_4,$$

   where $m_4 > 0$, $b_4 \geq 0$, and $0 < c_{\delta_4}(\mu_4) < (\mu_4)_f$ for all μ_4.

   We now assume now that death rate depends on maturity level and cellular iron level, as below:

   $$\delta_4(\mu_4, \gamma) = \left(\delta_4^{max} - \delta_4^{min}\right) \cdot \frac{\left(c_{\delta_4}(\mu_4)\right)^{k_{\delta_4}}}{\left(c_{\delta_4}(\mu_4)\right)^{k_{\delta_4}} + \left(\gamma\right)^{k_{\delta_4}}} + \delta_4^{min}.$$

   Notice that when γ is relatively small, $\delta_4(\mu_4, \gamma)$ is close to δ_4^{max}, and when γ is relatively large, $\delta_4(\mu_4, \gamma)$ is close to δ_4^{min}. The "relativity" is affected by $c_{\delta_4}(\mu_4)$. As cells mature through class P_4 (i.e., as μ_4 increases), the value of $c_{\delta_4}(\mu_4)$ increases, which means that the death rate for a given iron level γ also increases. (Note that we choose $k_{\delta_4} > 1$). Hence, a cell having only a little iron when it arrives in class P_4 is less likely to die than a cell with that same level of iron that is about to mature out of class P_4. Figure 7 illustrates the relationship between $\delta_4(\mu_4, \gamma)$ and the structure variables μ_4 and γ.

5. Cells in class P_4 continue to collect iron and synthesize hemoglobin [18, 23] at a rate $h_4(Fe_{pl}, \gamma)$, which is explained in Section 4.7.

Thus, using equation (1), the state equation for class P_4 becomes

$$\frac{\partial}{\partial t}P_4(t,\mu_4,\gamma) = -\delta_4(\mu_4,\gamma)P_4(t,\mu_4,\gamma) - \rho_4\frac{\partial}{\partial \mu_4}P_4(t,\mu_4,\gamma) - \frac{\partial}{\partial \gamma}\Big[h_4(Fe_{pl},\gamma)P_4(t,\mu_4,\gamma)\Big]. \tag{9}$$

The initial condition for these cells can be given by

$$P_4(0,\mu_4,\gamma) = P_4^{init}(\mu_4,\gamma)$$

for $(\mu,\gamma) \in (0,(\mu_4)_f] \times [0,\gamma_f]$.

The boundary condition along the $\mu_4 = 0$ boundary is given by

$$P_4(t,0,\gamma) = P_4^{bdy,\mu}(t,\gamma) = P_3(t,(\mu_3)_f,\gamma), \tag{10}$$

for $\gamma \in [0,\gamma_f]$. This ensures continuity as cells mature from class P_3 into class P_4.

The $\gamma = 0$ boundary condition is given by

$$h_4(Fe_{pl},0)P_4(t,\mu_4,0) = 0. \tag{11}$$

for $\mu_4 \in [0,(\mu_4)_f]$. As was the case for class P_3, this is a zero-flux boundary condition.

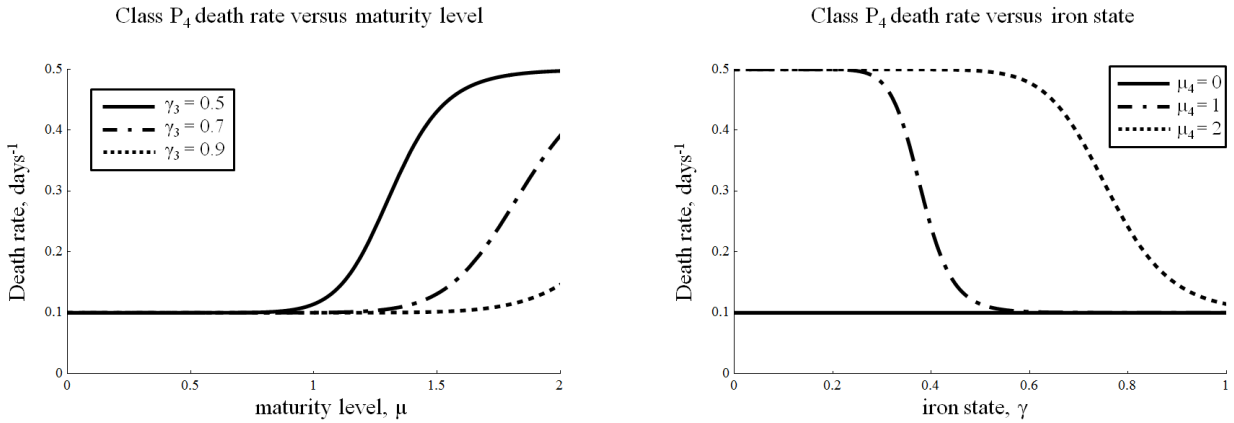


Figure 7: Death rate in class P_4 is a function of both maturity level, μ_4, and cellular iron state, γ. For a fixed maturity level μ_4, death rate decreases as iron state γ increases. That is, for a given maturity level, cells with little iron are more likely to die. For a given iron state $\gamma < c_{\delta_4}(\mu_4)$, death rate increases as maturity level increases. These plots were generated with parameter values $\delta_4^{min} = 0.1$, $\delta_4^{max} = 0.5$, $m_4 = 0.38$, $b_4 = 0$, and $k_{\delta_4} = 12$.

4.6 Class P_5

The cells in class P_5 include mature erythrocytes and circulating reticulocytes. We make the following assumptions about cells in class P_5.

1. The maturation rate ρ_5 is constant.
2. The average life span of a red blood cell in a patient with chronic kidney disease is about 70 days, significantly shorter than for healthy persons [25, 40, 42]. We set the maximum maturity level to be $(\mu_5)_f = 100$, but the death rate is set such that virtually no cells reach the maximum maturity level.
3. As they have no nuclei, cells in this stage do not proliferate [18], and therefore $\beta_5 = 0$.
4. Death rate in this class is assumed to have four components: death due to low cellular iron, death due to aging, death due to neocytolysis, and death due to blood loss.

   (a) *Death due to low cellular iron.* As in the previous class, cells that lack a full complement of iron have increased mortality. As in class P_4, we have

   $$c_{\delta_{5,\gamma}}(\mu_5) = m_5\mu_5 + b_5, \qquad m_5 > 0,$$

   and

   $$\delta_{5,\gamma}(\mu_5,\gamma) = \left(\delta_{5,\gamma}^{max} - \delta_{5,\gamma}^{min}\right) \cdot \frac{\left(c_{\delta_{5,\gamma}}(\mu_5)\right)^{k_{\delta_{5,\gamma}}}}{\left(c_{\delta_{5,\gamma}}(\mu_5)\right)^{k_{\delta_{5,\gamma}}} + \left(\gamma\right)^{k_{\delta_{5,\gamma}}}} + \delta_{5,\gamma}^{min}.$$

   (b) *Death due to aging.* Senescent (aged) erythrocytes are enveloped and destroyed in the spleen [18], so death rate in this class is also a function of maturity level. This process occurs independent of cellular iron state.

   $$\delta_{5,\mu}(\mu_5) = \left(\delta_{\mu_5}^{min} - \delta_{\mu_5}^{max}\right) \cdot \frac{\left(c_{\delta_{\mu_5}}\right)^{k_{\delta_{\mu_5}}}}{\left(c_{\delta_{\mu_5}}\right)^{k_{\delta_{\mu_5}}} + \left(\mu_5\right)^{k_{\delta_{\mu_5}}}} + \delta_{\mu_5}^{max}$$

   (c) *Death due to neocytolysis.* Neocytolysis targets RBCs between 14-21 days old (i.e., for maturity level $14 \leq \mu_5 \leq 21$) [4, 33]. These cells have increased death rate when EPO level drops, but it is not yet known whether the mechanisms that cause this increase in death rate are related to a large drop in EPO level (i.e., a large negative rate of change of EPO level) and/or simply a low EPO level. We account for both in this model, with tuning parameters α_1 and α_2 to account for the relative effects.

   We begin with the assumption that neocytolysis is a response to low EPO level. We choose a decreasing sigmoid function for the maximum death rate:

   $$\delta_{5,neo,1}^{max}(EPO) = \delta_{5,neo}^{max,1} \cdot \frac{\left(c_{\delta_5}^{neo}\right)^{k_{\delta_5}^{neo}}}{\left(c_{\delta_5}^{neo}\right)^{k_{\delta_5}^{neo}} + \left(EPO\right)^{k_{\delta_5}^{neo}}}.$$

   Then the death rate is given by

   $$\delta_{5,neo,1}(\mu_5, EPO) = \delta_{5,neo,1}^{max}(EPO)\left[\frac{1}{1+e^{-2k_{h,1}(\mu_5-15)}} - \frac{1}{1+e^{-2k_{h,1}(\mu_5-20)}}\right],$$

the sum of smoothed heaviside functions. Note that when $k_{h,1}$ is sufficiently large, the death rate is zero when $\mu_5 < 14$ and $\mu_5 > 21$. Also, for maturity levels $14 \leq \mu_5 \leq 21$, when EPO level is small, the maximum death rate is large. Figure 8 depicts the output of the death rate function $\delta_{5,neo,1}(\mu_5, EPO)$, for both the case of a fixed maturity level with varying EPO and the case of fixed EPO with varying maturity level.

For the assumption that neocytolysis is a response to large negative rate of change of EPO, we choose a decreasing function for the maximum death rate:

$$\delta_{5,neo,2}^{max}\left(\frac{d}{dt}EPO\right) = \delta_{5,neo}^{max,2}\left[1 - \frac{1}{1+e^{-2k_{h,3}(\frac{d}{dt}EPO - \rho_{EPO,crit})}}.\right]$$

(Note here that we do not use a sigmoid function (as we did for $\delta_{5,neo,1}^{max}(EPO)$) because the area of interest includes negative values of $\frac{d}{dt}EPO$.) The death rate, given by

$$\begin{aligned}&\delta_{5,neo,2}\left(\mu_5, \frac{d}{dt}EPO\right)\\ &\quad = \delta_{5,neo,2}^{max}\left(\frac{d}{dt}EPO\right)\left[\frac{1}{1+e^{-2k_{h,2}(\mu_5-15)}} - \frac{1}{1+e^{-2k_{h,2}(\mu_5-20)}}\right],\end{aligned}$$

is plotted in Figure 9 for both the constant EPO rate with varying maturity case and the constant maturity level with varying EPO rate case.

Then the death rate due to neocytolysis is given by

$$\delta_{5,neo}\left(\mu_5, EPO, \frac{d}{dt}EPO\right) = \alpha_1\delta_{5,neo,1}\left(\mu_5, EPO\right) + \alpha_2\delta_{5,neo,2}\left(\mu_5, \frac{d}{dt}EPO\right).$$

(d) *Death due to blood loss.* We make a separate death rate to account for losses such as blood lost during blood draws, denoted $\delta_{5,loss}(t, \mu_5)$. The iron from these losses is not recycled.

We assume that these phenomena occur independently and that the resultant death rate for class P_5 is the sum of these four components,

$$\begin{aligned}\delta_5\left(\mu_5, \gamma, EPO, \frac{d}{dt}EPO\right) &= \delta_{5,\gamma}(\mu_5, \gamma) + \delta_{5,\mu}(\mu_5)\\ &\quad + \delta_{5,neo}\left(\mu_5, EPO, \frac{d}{dt}EPO\right) + \delta_{5,loss}(t, \mu_5).\end{aligned}$$

5. Only reticulocytes at this stage are still able to collect iron, and at a smaller rate than previous cell classes [10, 16, 18]. The hemoglobinization rate $h_5(Fe_{pl}, \gamma)$ for cells in class P_5 is discussed in Section 4.7.

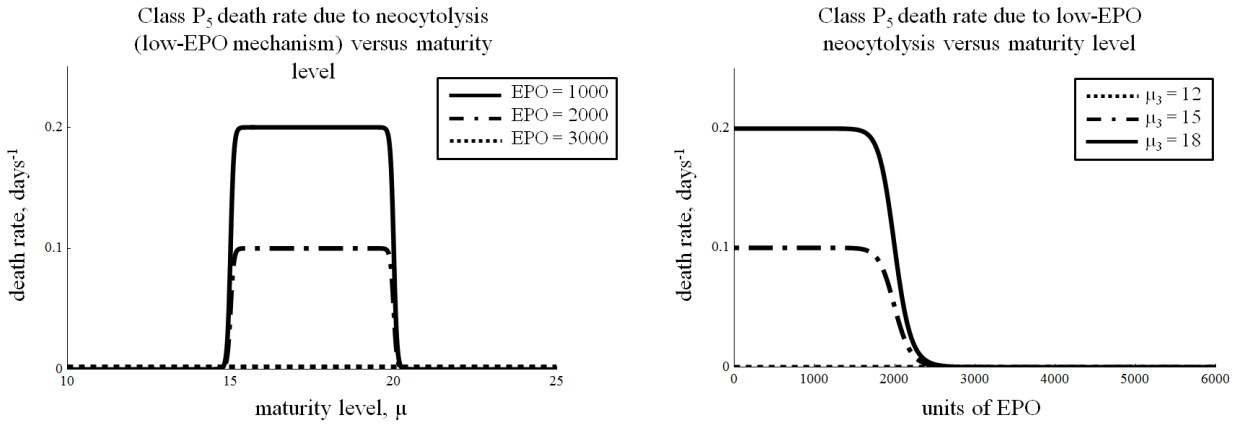


Figure 8: Low-EPO neocytolysis death rate in class P_5 is a function of maturity level μ_5 and EPO level. In the first plot, we fix EPO and show the death rate over varying maturity level. Notice that neocytolysis affects cells such that $14 \leq \mu_5 \leq 21$. Also, as EPO increases, the effects of neocytolysis diminish. This fact is demonstrated again in the second plot. To produce these plots, we chose parameter values $\delta_{5,neo}^{max,1} = 0.2$, $c_{\delta_5}^{neo} = 2000$, $k_{\delta_5}^{neo} = 20$ and $k_{h,1} = 10$.

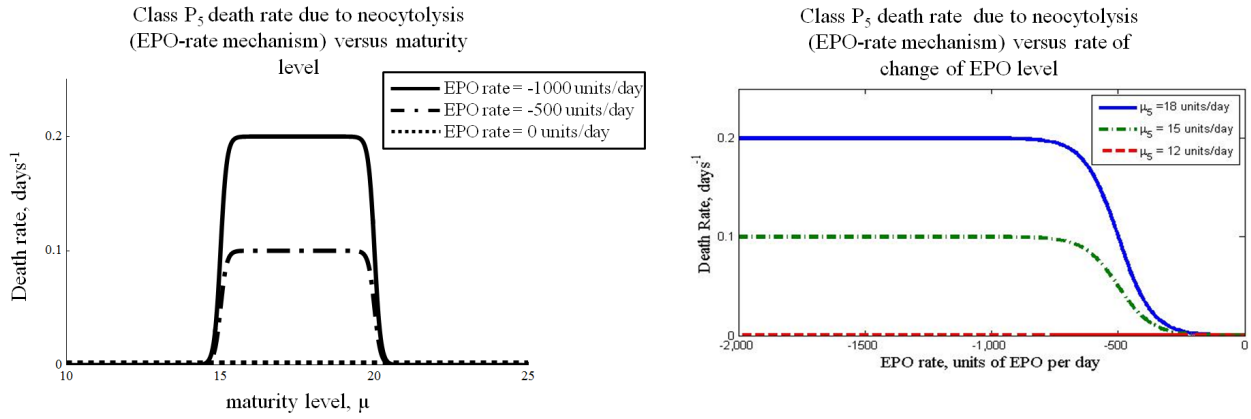


Figure 9: Large negative EPO rate neocytolysis death rate in class P_5 is a function of maturity level μ_5 and EPO rate. Note that neocytolysis targets cells with maturity level $14 \leq \mu_5 \leq 21$. As EPO rate attains large negative values, the death rate due to neocytolysis increases. To produce these plots, we chose parameter values $\delta_{5,neo}^{max,2} = 0.2$, $k_{h,3} = 0.0075$, $\rho_{EPO,crit} = -500$ and $k_{h,2} = 5$.

Using equation (1), the equation governing cells in class P_5 is therefore given by

$$\frac{\partial}{\partial t}P_5(t,\mu_5,\gamma) = -\delta_5\left(\mu_5,\gamma,EPO,\frac{d}{dt}EPO\right)P_5(t,\mu_5,\gamma) - \rho_5\frac{\partial}{\partial\mu_5}P_5(t,\mu_5,\gamma) - \frac{\partial}{\partial\gamma}\Big[h_5(Fe_{pl},\gamma)P_5(t,\mu_5,\gamma)\Big]. \tag{12}$$

The initial condition for these cells can be given by

$$P_5(0,\mu_5,\gamma) = P_5^{init}(\mu_5,\gamma)$$

for $(\mu_5,\gamma)\in(0,(\mu_5)_f]\times[0,\gamma_f]$. The $\mu_5=0$ boundary condition is given by

$$P_5(t,0,\gamma) = P_4(t,(\mu_4)_f,\gamma) \tag{13}$$

for $\gamma\in[0,\gamma_f]$, and the $\gamma=0$ boundary condition is given by

$$h_5(Fe_{pl},0)P_5(t,\mu_5,0) = 0. \tag{14}$$

4.7 Hemoglobinization

Cells in classes P_3, P_4 and P_5 participate in iron uptake for the purposes of synthesizing hemoglobin. As noted earlier, we use γ as a structure variable that indicates the amount of iron in a given cell. Moreover, recall that $0\le\gamma\le\gamma_f=2$, where $\gamma_{full}=1$ represents the amount of iron the "typical" RBC contains in a healthy individual. Finally, recall that when a cell divides, we assume that each of the daughter cells receives half of the parent cell's iron endowment.

In order to determine the rate at which iron moves from the iron compartment into RBCs, we compare the amount of iron required for cells to be hemoglobinized at the maximum rate with the amount of iron available in the blood plasma (i.e., iron in the blood plasma compartment). Then we can determine if there is sufficient iron available to hemoglobinize at the maximum rate or if hemoglobinization is occurring in an iron-restricted fashion.

We assume that when there is an abundance of iron available, cells can obtain a full complement of iron in three days [18]. Cells begin the hemoglobinization process in class P_3. Cells reside in this class for one day and they undergo cell division at a rate of 1 division per day. After cells transition out of class P_3, they no longer undergo cell division (i.e., cells in classes P_4 and P_5 do not divide). While we model hemoglobinization and proliferation as continuous processes, the following considerations in discrete time nodes indicate that the maximum rate of iron uptake should be set to approximately $\frac{2}{5}\gamma_{full}$ iron level units per day so that a cell could attain a full iron complement in three days' time.

$$\begin{aligned}
\text{day 0:} &\quad \gamma = 0\\
\text{day 1 before cell division:} &\quad \gamma = \tfrac{2}{5}\gamma_{full} = \tfrac{2}{5}\\
\text{day 1 after cell division:} &\quad \gamma = \tfrac{1}{5}\gamma_{full} = \tfrac{1}{5}\\
\text{day 2:} &\quad \gamma = \tfrac{1}{5}\gamma_{full} + \tfrac{2}{5}\gamma_{full} = \tfrac{3}{5}\\
\text{day 3:} &\quad \gamma = \tfrac{3}{5}\gamma_{full} + \tfrac{2}{5}\gamma_{full} = 1
\end{aligned}$$

Cells in class P_4 can uptake iron at this rate until their iron state reaches γ_{full}, at which point they stop taking in iron. Reticulocytes in class P_5 (i.e., cells in class P_5 with maturity level $0\le\mu_5\le 2$) are circulating in the blood. While they are still capable of iron uptake until they reach iron state

$\gamma_{full} = 1$, the rate of uptake is smaller [18], so we multiply the rate for class P_4 by the constant $0 < k_5 < 1$. Therefore we define the maximum iron uptake rate functions h_3^{max}, h_4^{max}, and h_5^{max} by

$$h_3^{max}(\gamma) = \frac{2}{5}$$

$$h_4^{max}(\gamma) = \left(\frac{2}{5}\right) \cdot \frac{\left(\gamma_{full}\right)^{k_{h,4,max}}}{\left(\gamma_{full}\right)^{k_{h,4,max}} + \left(\gamma\right)^{k_{h,4,max}}} = \frac{2}{5} \cdot \frac{1}{1+\gamma^{k_{h,4,max}}}$$

$$h_5^{max}(\mu_5, \gamma) = \begin{cases} k_5 h_4^{max}(\gamma) & \text{for } 0 \le \mu_5 \le 2 \\ 0 & \text{for } \mu_5 > 2. \end{cases}$$

Each of these functions is depicted in Figure 10.

The rate of iron needed if every cell takes up iron at its maximum rate can therefore be computed as

$$\begin{aligned} \rho_{Fe,needed} &= (\text{max rate iron needed in class } P_3) + (\text{max rate iron needed in class } P_4) \\ &\quad + (\text{max rate iron needed in class } P_5) \\ &= k_{Fe}\Bigg[\int_0^{\gamma_f}\int_0^{(\mu_3)_f} h_3^{max}(\gamma) P_3(t,\mu_3,\gamma)\, d\mu_3\, d\gamma \\ &\qquad + \int_0^{\gamma_f}\int_0^{(\mu_4)_f} h_4^{max}(\gamma) P_4(t,\mu_4,\gamma)\, d\mu_4\, d\gamma \\ &\qquad\quad + \int_0^{\gamma_f}\int_0^{(\mu_5)_f} h_5^{max}(\mu_5,\gamma) P_5(t,\mu_5,\gamma)\, d\mu_5\, d\gamma\Bigg], \end{aligned}$$

where k_{Fe} is the amount of iron in one billion red blood cells with a full iron endowment.

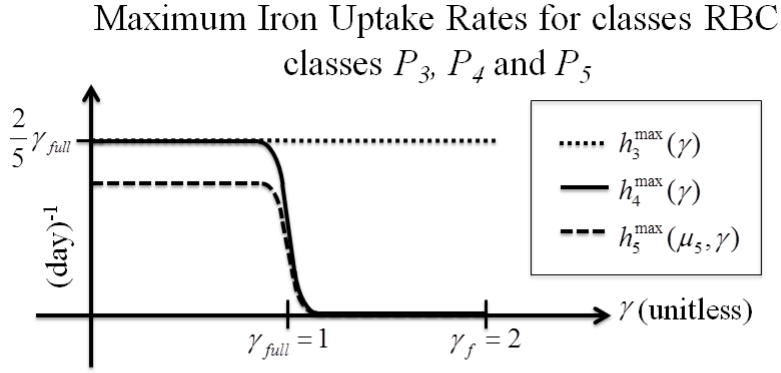


Figure 10: Maximum iron uptake rates where $0 \le \mu_5 \le 2$.

We compare this with the rate of iron available for hemoglobinization at time t. We assume that the iron available is proportional to amount of iron in the blood plasma compartment. Hence, the rate of iron availability is given by

$$\rho_{Fe,avail} = k_{Fe,eff} Fe_{pl}(t), \tag{15}$$

for some $k_{Fe,eff} > 0$.

We define the iron availability rate fraction, $0 \leq k_{Fe,avail} \leq 1$, to be

$$k_{Fe,avail} = \begin{cases} 1 & \text{for } \rho_{Fe,needed} \leq \rho_{Fe,avail} \\ \dfrac{\rho_{Fe,avail}}{\rho_{Fe,needed}} & \text{for } \rho_{Fe,needed} > \rho_{Fe,avail}. \end{cases}$$

Then the actual rates of iron uptake are given by

$$h_i(Fe_{pl}, \gamma) = k_{Fe,avail} h_i^{max}(\gamma), \qquad i = 3, 4, 5.$$

4.8 EPO compartment

While healthy individuals produce EPO in response to a decrease in blood oxygen, patients with poorly functioning kidneys produce only a small basal level of EPO in the kidney and liver [22]. They receive rHuEPO intravenously during their dialysis treatments. In this model, we assume the use of a bioidentical rHuEPO; that is, we will not distinguish between rHuEPO and endogenous EPO with respect to their action.

We assume the rate of endogenous EPO production in the liver and kidney to be constant. We also assume that EPO clearance is proportional to the amount of EPO present. Thus we have

$$\frac{d}{dt} EPO(t) = \rho_{EPO,endog} + \rho_{EPO,exog}(t) - \frac{\ln 2}{t_{1/2}} EPO(t), \tag{16}$$

with initial condition

$$EPO(0) = E_0,$$

where $\rho_{EPO,endog}$ is the (assumed constant) rate of endogenous EPO production, $\rho_{EPO,exog}(t)$ is the rate of exogenous EPO provided during treatment, and $t_{1/2}$ is the half-life of EPO.

5 Iron Model

We now introduce the second portion of our model, the iron compartments. Iron is required to make hemoglobin, the protein that gives erythrocytes the ability to carry oxygen. It is also the protein that gives erythrocytes their characteristic red color. If iron is not available during erythropoiesis, the result is lighter-colored (hypochromic) erythrocytes with reduced capacity to carry oxygen.

Control of iron in the body is a strictly regulated process, in part because there is no pathway for the excretion of excess iron [17, 46]. When red blood cells age, they become enveloped by macrophages in the spleen. The iron from their hemoglobin is then recaptured and sent to the bone marrow for use in making hemoglobin for new erythrocytes. This recycling process is very efficient and is the main source of iron for erythropoiesis [41]. In much smaller quantities, iron is absorbed from diet and is transferred in and out of storage in the liver. The only losses to the system are from sweating, cells being shed, blood losses, etc.

The major regulator of iron homeostasis is the hormone hepcidin, which is produced in the liver [17, 31, 46]. Hepcidin's role in iron homeostasis has only recently been studied, and therefore the

mechanisms and pathways leading to the production and action of hepcidin are only beginning to be understood.

The protein ferroportin is required to transport iron out of a cell and into the plasma. Hepcidin binds to ferroportin and causes the complex to be absorbed into the cell, effectively interrupting the transport of iron into the blood plasma, as depicted in Figure 11. Hence, an increase in hepcidin level causes iron to remain in cells and prevents its release into the blood plasma (where it could be used in RBC production).

Hepcidin production is increased in response to high iron level in the blood plasma and/or liver and is decreased in response to erythropoietic activity [17, 31]. Production is also increased in the presence of certain cytokines which are released due to inflammation in the body [17, 46]. It is thought that this might be a defense mechanism against foreign organisms which may need iron to reproduce. Since patients in ESRD commonly have other health problems, they often have higher than normal levels of inflammation. Thus, they may produce higher than normal levels of hepcidin and as a result, even if there is enough iron in the body, it may not be available for erythropoiesis because it cannot leave the cells and enter the plasma [1].

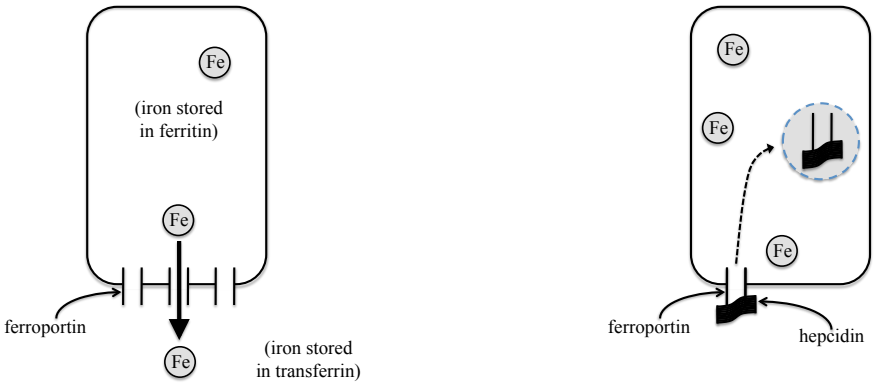
We propose a model of ordinary differential equations for the iron model using the conceptual model shown in Figure 12. Note that, for the purposes of our model, all rates of iron transfer are scaled such that they assume units of mg iron per day.

5.1 Hepcidin

The state variable $H(t)$ represents plasma hepcidin level at time t, with

$$0 \leq H(t) \leq 1.$$

A hepcidin level of 0 indicates little or no hepcidin present. In this situation, iron can pass unencumbered across a cell membrane and enter the iron in the blood plasma compartment. A hepcidin level of 1 indicates a maximum hepcidin level; when hepcidin is at its maximum level, iron cannot cross a



(a) Ferroportin is required for the transport of iron out of cells.

(b) Hepcidin is the major regulator of iron transport out of cells.

Figure 11: Iron regulation at a cellular level.

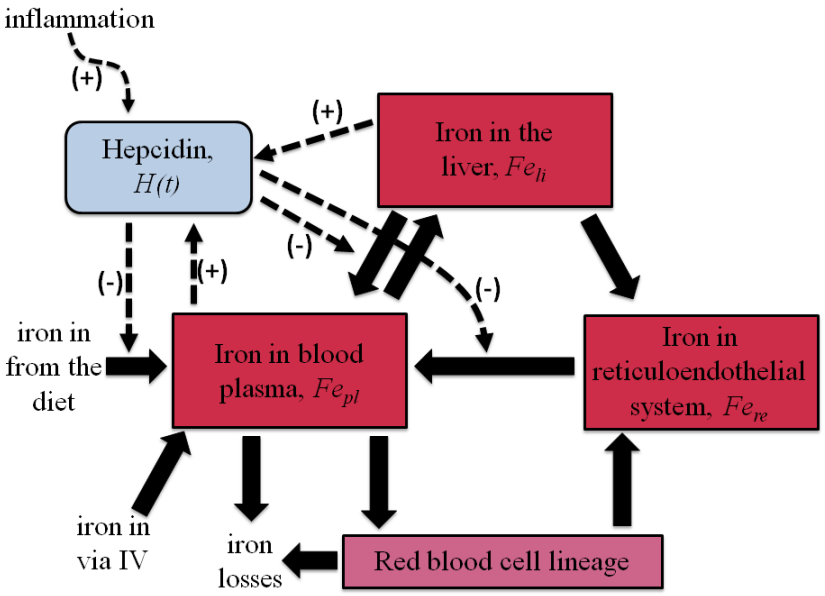


Figure 12: Iron Model. Note that the states variables are H, Fe_{li}, Fe_{pl} and Fe_{re}.

cell membrane to enter the blood plasma. In order to ensure that $0 \leq H \leq 1$, we use characteristic functions that are "turned on" when a condition is true and "off" when it is false. For example,

$$\chi_{\{H<1\}}(t) = \chi_{\{\tau | H(\tau)<1\}}(t) = \begin{cases} 1 & \text{for } H(t) < 1 \\ 0 & \text{for } H(t) \geq 1. \end{cases}$$

We assume the following:

1. Hepcidin is produced in response to high levels of iron; how this is measured by the body is unclear. We assume that production is increased in response to high levels in both the liver and in the plasma. The relative size of these two responses can be adjusted by way of the nonnegative rate constants $k_{Fe,pl}$ and $k_{Fe,li}$, so

   $$[\text{rate of increase in hepcidin due to high level of iron in plasma}] = k_{Fe,pl} Fe_{pl}(t) \chi_{\{H<1\}}$$

   and

   $$[\text{rate of increase in hepcidin due to high level of iron in liver}] = k_{Fe,li} Fe_{li}(t) \chi_{\{H<1\}}.$$

   The characteristic functions in these terms allow hepcidin level to increase to $H = 1$ in response to high level of iron in the plasma or liver, but do not allow hepcidin to exceed this level.

2. Hepcidin production is increased in the presence of inflammation, but the specific pathways that cause this response are still under investigation. We assume that the input $I(t)$ is a measure of the overall inflammation state of the body (a broad simplification that should be revisited in future models) such that $0 \leq I(t) \leq 1$. Therefore,

   $$[\text{rate of increase in hepcidin due to inflammation}] = k_{infl} I(t) \chi_{\{H<1\}},$$

   where $k_{infl} \geq 0$.

3. While hepcidin is actually "consumed" as it is used to prevent the action of ferroportin, we initially assume a clearance proportional to the amount present. Thus,

$$[\text{rate of decrease in hepcidin}] = k_H H(t)\chi_{\{H>0\}}(t),$$

where $k_H \geq 0$.

Hence, we model hepcidin level by

$$\begin{aligned}\frac{dH}{dt}(t) = {} & k_{infl} I(t)\chi_{\{H<1\}}(t) + k_{Fe,pl} Fe_{pl}(t)\chi_{\{H<1\}}(t) + k_{Fe,li} Fe_{li}(t)\chi_{\{H<1\}}(t) \\ & - k_H H(t)\chi_{\{H>0\}}(t). \end{aligned} \tag{17}$$

We assume an initial hepcidin level of $H(0) = H_0$.

5.2 Iron in the reticuloendothelial system

The reticuloendothelial system consists of macrophages in the spleen and other cells that collect/envelop old and damaged cells and reclaim their iron. This includes any cell in the red blood cell lineage that dies, as well as liver cells that become senescent and/or damaged.

Based on our model for RBC dynamics, the rate of iron into the reticuloendothelial system from RBC lineage is

$$\begin{aligned} k_{Fe}\Bigg[& \int_0^{\gamma_f}\int_0^{(\mu_3)_f} \delta_3(\mu_3, EPO)\gamma P_3(t,\mu_3,\gamma)\, d\mu_3\, d\gamma \\ & + \int_0^{\gamma_f}\int_0^{(\mu_4)_f} \delta_4(\mu_4, EPO)\gamma P_4(t,\mu_4,\gamma)\, d\mu_4\, d\gamma \\ & + \int_0^{\gamma_f}\int_0^{(\mu_5)_f} \Big[\delta_{5,\gamma}(\mu_5,\gamma) + \delta_{5,\mu}(\mu_5) \\ & \qquad + \delta_{5,neo}\left(\mu_5, EPO, \frac{d}{dt}EPO\right)\Big]\gamma P_5(t,\mu_5,\gamma)\, d\mu_5\, d\gamma\Bigg], \end{aligned}$$

where k_{Fe} is once again the amount of iron in one billion red blood cells with a full iron endowment. Notice that for class P_5 we do not recycle iron from deaths due to blood losses.

The liver serves as a storage area for iron. Iron residing in liver cells that die is recaptured and ends up in the reticuloendothelial system. Hence, we assume that

$$[\text{rate of iron into the reticuloendothelial system from the liver}] = k_{li\to re} Fe_{li}(t),$$

where $k_{li\to re} \geq 0$.

Reticuloendothelial cells require ferroportin to transfer iron from within the cell into the blood plasma. Hepcidin negatively regulates this transport; when hepcidin level is high, the amount of iron that can leave the reticuloendothelial system and enter the blood plasma is low. We assume that

$$[\text{rate of iron out of the reticuloendothelial system into the blood plasma}] = k_{re\to pl}(1 - H(t))Fe_{re}(t),$$

where $k_{re\to pl} \geq 0$.

Thus, we have

$$\begin{aligned}\frac{dFe_{re}}{dt} = k_{Fe}\Bigg[&\int_0^{\gamma_f}\int_0^{(\mu_3)_f} \delta_3(\mu_3, EPO)\gamma P_3(t,\mu_3,\gamma)\,d\mu_3\,d\gamma \\ &+ \int_0^{\gamma_f}\int_0^{(\mu_4)_f} \delta_4(\mu_4, EPO)\gamma P_4(t,\mu_4,\gamma)\,d\mu_4\,d\gamma \\ &+ \int_0^{\gamma_f}\int_0^{(\mu_5)_f} \left[\delta_{5,\gamma}(\mu_5,\gamma) + \delta_{5,\mu}(\mu_5) + \delta_{5,neo}\left(\mu_5, EPO, \frac{d}{dt}EPO\right)\right]\gamma P_5(t,\mu_5,\gamma)\,d\mu_5\,d\gamma\Bigg] \\ &+ k_{li\to re}Fe_{li} - k_{re\to pl}(1-H)Fe_{re}. \end{aligned} \tag{18}$$

We assume an initial condition of $Fe_{re}(0) = Fe_{re}^{init}$ mg of iron.

5.3 Iron in the Liver

Iron enters the liver (for storage) from the blood plasma when the level of iron in the blood plasma is high and leaves storage when the level of iron in the blood plasma is low. The maximum rate of iron transfer between the liver and the blood plasma is assumed to be k_{max}, and we model these rates with sigmoid functions. Thus,

$$[\text{rate of iron into liver from the blood plasma compartment}] = K_{pl\to li}\left(Fe_{pl}(t)\right)Fe_{pl}(t),$$

where

$$K_{pl\to li}\left(Fe_{pl}\right) = k_{max}\left(1 - \frac{\left(c_{pl\to li}\right)^{k_{pl\to li}}}{\left(c_{pl\to li}\right)^{k_{pl\to li}} + \left(Fe_{pl}\right)^{k_{pl\to li}}}\right)$$

and

$$[\text{rate of iron out of the liver into the blood plasma}] = K_{li\to pl}\left(Fe_{pl}(t)\right)\left(1-H(t)\right)Fe_{li}(t)$$

where

$$K_{li\to pl}\left(Fe_{pl}\right) = k_{max}\left(\frac{\left(c_{li\to pl}\right)^{k_{li\to pl}}}{\left(c_{li\to pl}\right)^{k_{li\to pl}} + \left(Fe_{pl}\right)^{k_{li\to pl}}}\right).$$

Notice that $1-H(t)$ appears in the expression for rate of iron into the blood plasma compartment from the liver compartment because hepcidin inhibits the action of ferroportin in allowing the transport of iron out of the liver. The shapes of the functions $K_{pl\to li}$ and $K_{li\to pl}$ are illustrated in Figure 13.

When cells in the liver die, the iron in those cells is collected by cells in the reticuloendothelial system. We model this as

$$[\text{rate of iron out of the liver into the reticuloendothelial system}] = k_{li\to re}Fe_{li}(t).$$

Taking into account all of the above-described rates, the total time rate of change of iron in the liver is given by

$$\frac{dFe_{li}}{dt} = K_{pl\to li}\left(Fe_{pl}(t)\right)Fe_{pl}(t) - K_{li\to pl}\left(Fe_{pl}(t)\right)\left(1-H(t)\right)Fe_{li}(t) - k_{li\to re}Fe_{li}(t). \tag{19}$$

We assume an initial condition of $Fe_{li}(0) = Fe_{li}^{init}$ mg of iron.

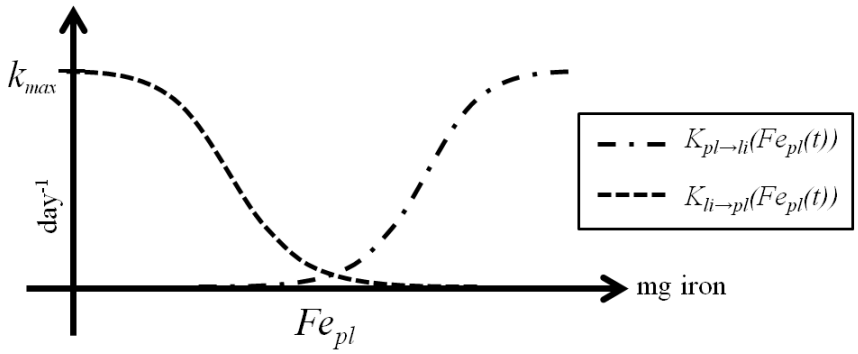


Figure 13: Rate coefficients for iron in and out of storage (i.e., iron into the liver from the blood plasma and iron into the blood plasma from the liver).

5.4 Iron in the Blood Plasma

The blood plasma is the main source of iron for erythropoiesis. As mentioned previously, dialysis patients typically received intravenous iron treatments. Iron also enters the blood plasma from the reticuloendothelial system and the liver, and via the intestines due to dietary consumption. Since each of these last three sources of iron depends on ferroportin to transfer the iron from within the cell to the plasma, the associated rates of transfer are all subject to the negative regulatory effect of hepcidin. Iron can leave the blood plasma whenever the patient loses any blood.

We assume that iron enters the plasma via the intestines due to dietary intake with a constant maximum rate given by $\rho_{iron,diet}$. Iron in intestinal cells must be transported into the blood plasma via ferroportin. Therefore, considering the effect of hepcidin on this transfer, we have

$$[\text{rate of iron into blood plasma from diet}] = k_{diet}(1 - H(t))\rho_{iron,diet},$$

where $0 \leq k_{diet} \leq 1$.

We assume the rate at which iron is transferred into the plasma is given by $\rho_{Fe,ex}(t)$ and the rate at which iron is transferred out of the plasm due to blood loss is $\rho_{Fe,pl,loss}(t)$. The rates at which iron is transferred (i) into blood plasma from the reticuloendothelial system, (ii) into the blood plasma from the liver, (iii) into the liver from the blood plasma, and (iv) into the red blood cell lineage were

all described previously. Thus, we have the following equation for iron in the blood plasma:

$$\begin{aligned}
\frac{dFe_{pl}}{dt} &= [\text{rate of iron into blood plasma from diet}] \\
&\quad + [\text{rate of iron into blood plasma from reticuloendothelial system}] \\
&\quad + [\text{rate of iron into blood plasma from liver}] \\
&\quad + [\text{rate of iron into blood plasma from intravenous treatment}] \\
&\quad - [\text{rate of iron into liver from blood plasma}] \\
&\quad - [\text{rate of iron into RBC lineage from blood plasma}] \\
&\quad - [\text{rate of iron lost via blood losses}] \\
&= k_{diet}(1 - H(t))\rho_{iron,diet} \\
&\quad + k_{re\to pl}(1 - H(t))Fe_{re}(t) \\
&\quad + K_{li\to pl}(1 - H(t))Fe_{li}(t) \\
&\quad + \rho_{Fe,ex}(t) \\
&\quad - K_{pl\to li}(Fe_{pl})Fe_{pl}(t) \\
&\quad - k_{Fe,avail} \cdot \rho_{Fe,needed} \\
&\quad - \rho_{Fe,pl,loss}(t).
\end{aligned} \tag{20}$$

We assume an initial condition of $Fe_{pl}(0) = Fe_{pl}^{init}$ mg of iron.

6 Numerical Solution of Model Equations

Here we propose a numerical scheme for obtaining the states of the above-described model. These include the EPO level ($EPO(t)$), the RBC lineage states ($P_1(t,\mu_1)$, $P_2(t,\mu_2)$, $P_3(t,\mu_3,\gamma)$, $P_4(t,\mu_4,\gamma)$, and $P_5(t,\mu_5,\gamma)$), and the iron compartment states ($H(t)$, $Fe_{re}(t)$, $Fe_{li}(t)$, and $Fe_{pl}(t)$).

Equation (16), which describes EPO level, is an ordinary differential equation (ODE) that does not depend on any of the other states. Therefore, this equation (and its associated initial condition) are easily solved using any numerical ODE solver (e.g., MATLAB's `ode23`).

Equation (3), which describes the density of cells in class P_1 at various maturity levels, is a partial differential equation (PDE) that does not depend on any of the other states. To obtain a numerical solution for this state variable, we discretize with respect to the variable μ_1 to obtain a system of ODEs. These can then be solved (using the associated initial and boundary conditions) with any numerical ODE solver. The PDE (4) governing cells in class P_2 depends on $EPO(t)$, and its associated boundary condition depends on $P_1(t,(\mu_1)_f)$. Therefore, once we have numerical solutions for (16) and (3), we can solve (4) using the same method described for solving (3). A complete solution technique for the class P_1 and P_2 PDEs is described by the authors in [5], and will not be considered further here.

The remaining states are all interdependent, and the equations governing their dynamics must therefore be solved simultaneously. Each of the relevant sets of equations and initial/boundary conditions are considered in turn in the following sections.

6.1 Numerical Solution of Class P_3 PDE

6.1.1 Description of Initial-Value/Boundary-Value problem

The PDE (5) describing cells in class P_3 can be restated as

$$\frac{\partial}{\partial t}P_3(t,\mu,\gamma) = \chi_{\left[0,\frac{\gamma_f}{2}\right]}(\gamma)2\beta_3 P_3(t,\mu,2\gamma) - [\beta_3 + \delta_3(\mu, EPO)]P_3(t,\mu,\gamma) - \rho_3\frac{\partial}{\partial\mu}P_3(t,\mu,\gamma) - \frac{\partial}{\partial\gamma}\left[h_3(Fe_{pl})P_3(t,\mu,\gamma)\right]. \tag{21}$$

Here, we have replaced μ_3 by μ to simplify notation in the sections that follow. (In these sections, we will use subscripts on the variable μ to indicate discrete nodes on the interval $[0,(\mu_3)_f]$.) Also, in the above equation we have replaced $h_3(Fe_{pl},\gamma)$ by $h_3(Fe_{pl})$ to emphasize the fact that h_3 does not depend on iron level γ in this incarnation of our model. (See Section 4.7.)

Using the same convention for μ, the initial condition is given by

$$P_3(0,\mu,\gamma) = P_3^{init}(\mu,\gamma)$$

for $(\mu,\gamma) \in (0,\mu_f] \times [0,\gamma_f]$, where μ_f denotes the quantity originally described as $(\mu_3)_f$.

The $\gamma = 0$ boundary condition is given by

$$h_3(Fe_{pl})P_3(t,\mu,0) = 0 \tag{22}$$

for $\mu \in [0,\mu_f]$.

We choose to express the $\mu = 0$ boundary condition in the form

$$P_3(t,0,\gamma) = P_3^{bdy,\mu}(t,\gamma) = \begin{cases} P_2(t,(\mu_2)_f)\cdot\frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}\gamma^{a-1}(1-\gamma)^{b-1} & \text{for } \gamma\in[0,1] \\ 0 & \text{for } \gamma\in(1,\gamma_f]; \end{cases} \tag{23}$$

that is, $P_3(t,0,\gamma)/P_2(t,12)$ has a beta distribution with parameters a and b.

6.1.2 Mesh on "Spatial" Domain

We partition $[0,\mu_f]$ with N_μ equally-spaced nodes $\{0=\mu_1,\mu_2,\ldots,\mu_{N_\mu}=\mu_f\}$ using a step size

$$h_\mu = \frac{\mu_f}{(N_\mu - 1)}.$$

Similarly, we partition $[0,\gamma_f]$ with N_γ equally-spaced nodes $\{0=\gamma_1,\gamma_2,\ldots,\gamma_{N_\gamma}=\gamma_f\}$ using a step size

$$h_\gamma = \frac{\gamma_f}{(N_\gamma - 1)}.$$

We ensure that N_γ is odd so that a node exists at $\frac{\gamma_f}{2}$.

By pairing nodes from these two partitions, we can construct a mesh on $[0,\mu_f]\times[0,\gamma_f]$ consisting of the grid points $\{(\mu_i,\gamma_\ell) \mid i\in\{1,2,\ldots,N_\mu\} \text{ and } \ell\in\{1,2,\ldots,N_\gamma\}\}$.

6.1.3 Test Functions

We define piecewise linear functions of the form

$$\phi_k(x;h) = \begin{cases} \frac{1}{h}\Big(x-(k-2)h\Big), & \text{if } (k-2)h < x \le (k-1)h \\ \frac{1}{h}\Big(kh-x\Big), & \text{if } (k-1)h < x < kh \\ 0, & \text{otherwise} \end{cases}$$

and piecewise quadratic functions of the form

$$\chi_k(x;h) = \begin{cases} \frac{1}{h^2}\Big(x-(k-2)h\Big)\Big((k-1)h-x\Big), & \text{if } (k-2)h < x \le (k-1)h \\ \frac{1}{h^2}\Big(x-(k-1)h\Big)\Big(x-kh\Big), & \text{if } (k-1)h < x < kh \\ 0, & \text{otherwise.} \end{cases}$$

To obtain the weak formulation, we will use test functions of the form

$$\tilde{\phi}_k(x;h) = \phi_k(x;h) + \omega\chi_k(x;h),$$

where ω is an "upwinding" parameter for the relevant structure variable. We will use upwinding parameters ω_μ and ω_γ for the structure variables μ and γ, repectively.

To simplify notation in the discussion that follows, we will omit the h when it is obvious which value of h should be used; e.g., $\phi_j(\mu) \equiv \phi_j(\mu;h_\mu)$.

6.1.4 Weak Formulation

We multiply (21) by test functions $\tilde{\phi}_j(\mu)$ and $\tilde{\phi}_k(\gamma)$ and integrate over the entire spatial domain $[0,\mu_f]\times[0,\gamma_f]$ to obtain the weak formulation

$$\begin{aligned} &\int_0^{\mu_f}\int_0^{\gamma_f} \frac{\partial}{\partial t}P_3(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 1]} \\ &\qquad = 2\beta_3\int_0^{\mu_f}\int_0^{\frac{\gamma_f}{2}} P_3(t,\mu,2\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 2]} \\ &\qquad\quad -\int_0^{\mu_f}\int_0^{\gamma_f}\Big(\beta_3+\delta_3(\mu,EPO)\Big)P_3(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 3]} \\ &\qquad\quad -\rho_3\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\mu}P_3(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 4]} \\ &\qquad\quad -\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\gamma}\Big(h_3(Fe_{pl})P_3(t,\mu,\gamma)\Big)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 5].} \end{aligned} \tag{24}$$

6.1.5 Numerical Solution

Now, we assume that the approximate solution can be expressed in the form

$$\begin{aligned} P_3^a(t,\mu,\gamma) &= \sum_{i=1}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\ &= \sum_{\ell=1}^{N_\gamma} P_3(t,\mu_1,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\ &= \sum_{\ell=1}^{N_\gamma} P_3(t,0,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\ &= \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma), \end{aligned} \tag{25}$$

where $A_{i,\ell}(t)$ represents the approximate value of $P_3(t,\mu_i,\gamma_\ell)$. It is helpful to visualize the $N_\mu \times N_\gamma$ coefficient matrix $A(t)$ as an array of function values corresponding to a set of points in the region $[0,\mu_f]\times[0,\gamma_f]$; i.e., each entry $A_{i,\ell}(t)$ represents the value of P_3^a at time t at the grid point (μ_i,γ_ℓ):

$$\begin{array}{c} \\ (i=1) \\ (i=2) \\ \vdots \\ (i=N_\mu) \end{array} \begin{array}{c} \begin{array}{cccc} (\ell=1) & (\ell=2) & \cdots & (\ell=N_\gamma) \end{array} \\ \begin{bmatrix} A_{1,1}(t) & A_{1,2}(t) & \dots & A_{1,N_\gamma}(t) \\ A_{2,1}(t) & A_{2,2}(t) & \dots & A_{2,N_\gamma}(t) \\ \vdots & \vdots & & \vdots \\ A_{N_\mu,1}(t) & A_{N_\mu,2}(t) & \cdots & A_{N_\mu,N_\gamma}(t) \end{bmatrix} \end{array}$$

It should be pointed out, however, that each entry in the first row of this array is actually a known quantity based on the boundary condition (23). Thus, the array becomes

$$\begin{array}{c} \\ (i=1) \\ (i=2) \\ \vdots \\ (i=N_\mu) \end{array} \begin{array}{c} \begin{array}{cccc} (\ell=1) & (\ell=2) & \cdots & (\ell=N_\gamma) \end{array} \\ \begin{bmatrix} P_3^{bdy,\mu}(t,\gamma_1) & P_3^{bdy,\mu}(t,\gamma_2) & \dots & P_3^{bdy,\mu}(t,\gamma_f) \\ A_{2,1}(t) & A_{2,2}(t) & \dots & A_{2,N_\gamma}(t) \\ \vdots & \vdots & & \vdots \\ A_{N_\mu,1}(t) & A_{N_\mu,2}(t) & \cdots & A_{N_\mu,N_\gamma}(t) \end{bmatrix} \end{array}$$

Differentiating (25) with respect to time, we see that

$$\frac{\partial}{\partial t}P_3^a(t,\mu,\gamma) = \sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma), \tag{26}$$

where $\dot{A}_{i,\ell}(t)$ represents the approximate value of $\frac{\partial}{\partial t}P_3(t,\mu_i,\gamma_\ell)$ at each grid point of the mesh (except those on the $\mu=0$ boundary). Note that $P_3^{bdy,\mu}(t,\gamma)$ only depends on t through $P_2(t,(\mu_2)_f)$, so $\frac{\partial}{\partial t}P_3^{bdy,\mu}(t,\gamma)$ can be computed by taking the time derivative of $P_2(t,(\mu_2)_f)$. In practice a numerical solution P_2^a will be used, so a numerical approximation of this time derivative can be computed.

Our problem now consists of finding $\{A_{i,\ell}(t) \mid i\in\{2,3,\dots,N_\mu\} \text{ and } \ell\in\{1,2,\dots,N_\gamma\}\}$. This can be done by constructing and solving a system of ODEs consisting of a total of $(N_\mu-1)N_\gamma$

equations. To obtain the system of ODEs, we replace P_3 and $\frac{\partial}{\partial t}P_3$ in (24) by the approximations P_3^a and $\frac{\partial}{\partial t}P_3^a$ described in (25) and (26). For example, Term 1 in (24) becomes

$$\begin{aligned}
&\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial t}P_3^a(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu\\
&\quad=\int_0^{\mu_f}\int_0^{\gamma_f}\Big(\sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma)\Big)\\
&\qquad\qquad\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu\\
&\quad=\sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\int_0^{\mu_f}\int_0^{\gamma_f}\phi_1(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu\\
&\qquad\qquad+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\int_0^{\mu_f}\int_0^{\gamma_f}\phi_i(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu\\
&\quad=\sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\tilde{\phi}_j(\mu)\;d\mu\Big]\cdot\Big[\int_0^{\gamma_f}\phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\;d\gamma\Big]\\
&\qquad\qquad+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\tilde{\phi}_j(\mu)\;d\mu\Big]\cdot\Big[\int_0^{\gamma_f}\phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\;d\gamma\Big]\\
&\quad=\sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\;d\mu\Big]\\
&\qquad\qquad\cdot\Big[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\Big]\\
&\qquad\qquad+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\;d\mu\Big]\\
&\qquad\qquad\cdot\Big[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\Big].
\end{aligned}\tag{27}$$

Substituting P_3^a into Term 2 in (24), we obtain

$$\begin{aligned}
&2\beta_3\int_0^{\mu_f}\int_0^{\frac{\gamma_f}{2}}P_3^a(t,\mu,2\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu\\
&\quad=2\beta_3\int_0^{\mu_f}\int_0^{\frac{\gamma_f}{2}}\Big(\sum_{\ell=1}^{N_\gamma}P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(2\gamma)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(2\gamma)\Big)\\
&\qquad\qquad\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu\\
&\quad=2\beta_3\sum_{\ell=1}^{N_\gamma}P_3^{bdy,\mu}(t,\gamma_\ell)\int_0^{\mu_f}\int_0^{\frac{\gamma_f}{2}}\phi_1(\mu)\phi_\ell(2\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu\\
&\qquad\qquad+2\beta_3\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\int_0^{\mu_f}\int_0^{\frac{\gamma_f}{2}}\phi_i(\mu)\phi_\ell(2\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu
\end{aligned}$$

$$
\begin{aligned}
&= 2\beta_3 \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu\right] \cdot \left[\int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right] \\
&\qquad + 2\beta_3 \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu\right] \cdot \left[\int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right] \\
&= 2\beta_3 \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu\right] \\
&\qquad\qquad \cdot \left[\int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\chi_k(\gamma)\ d\gamma\right] \\
&\qquad + 2\beta_3 \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \phi_i(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_i(\mu)\chi_j(\mu)\ d\mu\right] \\
&\qquad\qquad \cdot \left[\int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\chi_k(\gamma)\ d\gamma\right]. \qquad (28)
\end{aligned}
$$

Substituting P_3^a into Term 3 in (24), we obtain

$$
\begin{aligned}
&- \int_0^{\mu_f}\int_0^{\gamma_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big) P_3^a(t,\mu,\gamma) \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = -\int_0^{\mu_f}\int_0^{\gamma_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big) \cdot \Big(\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma)\Big) \\
&\qquad\qquad \cdot \tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = -\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \int_0^{\mu_f}\int_0^{\gamma_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big)\phi_1(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\qquad - \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \int_0^{\mu_f}\int_0^{\gamma_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big)\phi_i(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = -\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big)\phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu\right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right] \\
&\qquad - \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big)\phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu\right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right]
\end{aligned}
$$

$$
\begin{aligned}
&= -\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\Bigg[\int_0^{\mu_f}\Big(\beta_3+\delta_3(\mu,EPO)\Big)\phi_1(\mu)\phi_j(\mu)\;d\mu \\
&\qquad\qquad +\omega_\mu\int_0^{\mu_f}\Big(\beta_3+\delta_3(\mu,EPO)\Big)\phi_1(\mu)\chi_j(\mu)\;d\mu\Bigg] \\
&\qquad\qquad\cdot\Bigg[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\Bigg] \\
&\quad -\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Bigg[\int_0^{\mu_f}\Big(\beta_3+\delta_3(\mu,EPO)\Big)\phi_i(\mu)\phi_j(\mu)\;d\mu \\
&\qquad\qquad +\omega_\mu\int_0^{\mu_f}\Big(\beta_3+\delta_3(\mu,EPO)\Big)\phi_i(\mu)\chi_j(\mu)\;d\mu\Bigg] \\
&\qquad\qquad\cdot\Bigg[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\Bigg]. \qquad (29)
\end{aligned}
$$

Before substituting P_3^a into Term 4 in (24), we integrate that term by parts to obtain

$$
\begin{aligned}
&-\rho_3\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\mu}P_3(t,\mu,\gamma)\cdot\tilde\phi_j(\mu)\cdot\tilde\phi_k(\gamma)\;d\gamma\;d\mu \\
&\quad=-\rho_3\int_0^{\gamma_f}\left[\int_0^{\mu_f}\frac{\partial}{\partial\mu}P_3(t,\mu,\gamma)\cdot\tilde\phi_j(\mu)\;d\mu\right]\cdot\tilde\phi_k(\gamma)\;d\gamma \\
&\quad=-\rho_3\int_0^{\gamma_f}\left[P_3(t,\mu,\gamma)\tilde\phi_j(\mu)\Big|_{\mu=0}^{\mu=\mu_f}-\int_0^{\mu_f}P_3(t,\mu,\gamma)\tilde\phi_j'(\mu)\;d\mu\right]\cdot\tilde\phi_k(\gamma)\;d\gamma \\
&\quad=-\rho_3\int_0^{\gamma_f}\left[P_3(t,\mu_f,\gamma)\tilde\phi_j(\mu=\mu_f)-P_3(t,0,\gamma)\tilde\phi_j(\mu=0)-\int_0^{\mu_f}P_3(t,\mu,\gamma)\tilde\phi_j'(\mu)\;d\mu\right]\cdot\tilde\phi_k(\gamma)\;d\gamma \\
&\quad=-\rho_3\int_0^{\gamma_f}\left[P_3(t,\mu_f,\gamma)\phi_j(\mu=\mu_f)-P_3(t,0,\gamma)\phi_j(\mu=0)-\int_0^{\mu_f}P_3(t,\mu,\gamma)\tilde\phi_j'(\mu)\;d\mu\right]\cdot\tilde\phi_k(\gamma)\;d\gamma,
\end{aligned}
$$

where we have used the fact that $\tilde\phi_j(x)=\phi_j(x)$ when x is a nodal point. Substituting the approximate solution, we then obtain

$$
\begin{aligned}
&-\rho_3\int_0^{\gamma_f}\left[P_3^a(t,\mu_f,\gamma)\phi_j(\mu=\mu_f)-P_3^a(t,0,\gamma)\phi_j(\mu=0)-\int_0^{\mu_f}P_3^a(t,\mu,\gamma)\tilde\phi_j'(\mu)\;d\mu\right]\cdot\tilde\phi_k(\gamma)\;d\gamma \\
&\quad=-\rho_3\int_0^{\gamma_f}\Bigg[\Big(\sum_{\ell=1}^{N_\gamma}P_3^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu=\mu_f)\phi_\ell(\gamma)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\phi_i(\mu=\mu_f)\phi_\ell(\gamma)\Big)\phi_j(\mu=\mu_f) \\
&\qquad\qquad-\Big(\sum_{\ell=1}^{N_\gamma}P_3^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu=0)\phi_\ell(\gamma)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\phi_i(\mu=0)\phi_\ell(\gamma)\Big)\phi_j(\mu=0) \\
&\qquad\qquad-\int_0^{\mu_f}\Big(\sum_{\ell=1}^{N_\gamma}P_3^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\phi_\ell(\gamma)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\phi_i(\mu)\phi_\ell(\gamma)\Big)\tilde\phi_j'(\mu)\;d\mu\Bigg]\cdot\tilde\phi_k(\gamma)\;d\gamma
\end{aligned}
$$

$$
\begin{aligned}
&= -\rho_3 \int_0^{\gamma_f} \Bigg[\Big(\sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_\ell(\gamma) \Big) \phi_j(\mu=\mu_f) - \Big(\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\phi_\ell(\gamma) \Big) \phi_j(\mu=0) \\
&\qquad\qquad - \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \Big[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big] \cdot \phi_\ell(\gamma) \\
&\qquad\qquad - \sum_{i=2}^{N_\mu} \sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \Big[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big] \cdot \phi_\ell(\gamma) \Bigg] \cdot \tilde{\phi}_k(\gamma)\ d\gamma \\
&= -\rho_3 \sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_j(\mu=\mu_f) \cdot \Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_3 \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\phi_j(\mu=0) \cdot \Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_3 \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big] \cdot \Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_3 \sum_{i=2}^{N_\mu} \sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \Big[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big] \cdot \Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&= -\rho_3 \sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_j(\mu=\mu_f) \cdot \Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_3 \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\phi_j(\mu=0) \cdot \Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_3 \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\phi_j'(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j'(\mu)\ d\mu \Big] \\
&\qquad\qquad \cdot \Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_3 \sum_{i=2}^{N_\mu} \sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \Big[\int_0^{\mu_f} \phi_i(\mu)\phi_j'(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_i(\mu)\chi_j'(\mu)\ d\mu \Big] \\
&\qquad\qquad \cdot \Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \Big] . \qquad (30)
\end{aligned}
$$

Before substituting P_3^a into Term 5 in (24), we integrate that term by parts to obtain

$$
\begin{aligned}
&- \int_0^{\mu_f} \int_0^{\gamma_f} \frac{\partial}{\partial\gamma} \Big(h_3(Fe_{pl})P_3(t,\mu,\gamma) \Big) \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\qquad = \int_0^{\mu_f} \Bigg[- \int_0^{\gamma_f} \frac{\partial}{\partial\gamma} \Big(h_3(Fe_{pl})P_3(t,\mu,\gamma) \Big) \cdot \tilde{\phi}_k(\gamma)\ d\gamma \Bigg] \cdot \tilde{\phi}_j(\mu)\ d\mu \\
&\qquad = \int_0^{\mu_f} \Bigg[- h_3(Fe_{pl})P_3(t,\mu,\gamma)\tilde{\phi}_k(\gamma)\Big|_{\gamma=0}^{\gamma=\gamma_f} + \int_0^{\gamma_f} h_3(Fe_{pl})P_3(t,\mu,\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma \Bigg] \cdot \tilde{\phi}_j(\mu)\ d\mu
\end{aligned}
$$

$$
\begin{aligned}
&= \int_0^{\mu_f} \Bigg[- h_3(Fe_{pl}) P_3(t,\mu,\gamma_f)\tilde{\phi}_k(\gamma=\gamma_f) + h_3(Fe_{pl}) P_3(t,\mu,0)\tilde{\phi}_k(\gamma=0) \\
&\qquad\qquad + \int_0^{\gamma_f} h_3(Fe_{pl}) P_3(t,\mu,\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma \Bigg] \cdot \tilde{\phi}_j(\mu)\ d\mu \\
&= \int_0^{\mu_f} \Bigg[- h_3(Fe_{pl}) P_3(t,\mu,\gamma_f)\phi_k(\gamma=\gamma_f) + \int_0^{\gamma_f} h_3(Fe_{pl}) P_3(t,\mu,\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma \Bigg] \cdot \tilde{\phi}_j(\mu)\ d\mu,
\end{aligned}
$$

where we have applied boundary condition (6) and used the fact that $\tilde{\phi}_k(x) = \phi_k(x)$ when x is a nodal point. Substituting the approximate solution, we then obtain

$$
\begin{aligned}
&\int_0^{\mu_f} \Bigg[- h_3(Fe_{pl}) P_3^a(t,\mu,\gamma_f)\phi_k(\gamma=\gamma_f) + \int_0^{\gamma_f} h_3(Fe_{pl}) P_3^a(t,\mu,\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma \Bigg] \cdot \tilde{\phi}_j(\mu)\ d\mu \\
&\quad = \int_0^{\mu_f} \Bigg[- h_3(Fe_{pl}) \Big(\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\phi_\ell(\gamma=\gamma_f) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\phi_i(\mu)\phi_\ell(\gamma=\gamma_f) \Big)\phi_k(\gamma=\gamma_f) \\
&\qquad + \int_0^{\gamma_f} h_3(Fe_{pl}) \Big(\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\phi_i(\mu)\phi_\ell(\gamma) \Big)\tilde{\phi}_k'(\gamma)\ d\gamma \Bigg] \cdot \tilde{\phi}_j(\mu)\ d\mu \\
&\quad = \int_0^{\mu_f} \Bigg[- h_3(Fe_{pl}) P_3^{bdy,\mu}(t,\gamma_f)\phi_1(\mu)\phi_k(\gamma=\gamma_f) - h_3(Fe_{pl}) \sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_i(\mu)\phi_k(\gamma=\gamma_f) \\
&\qquad + \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu) \cdot \Big[\int_0^{\gamma_f} h_3(Fe_{pl})\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma \Big] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\phi_i(\mu) \cdot \Big[\int_0^{\gamma_f} h_3(Fe_{pl})\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma \Big] \Bigg] \cdot \tilde{\phi}_j(\mu)\ d\mu \\
&\quad = -h_3(Fe_{pl}) P_3^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu \Big] \\
&\qquad - h_3(Fe_{pl}) \sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_k(\gamma=\gamma_f) \cdot \Big[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu \Big] \\
&\qquad + \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu \Big] \cdot \Big[\int_0^{\gamma_f} h_3(Fe_{pl})\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma \Big] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \Big[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu \Big] \cdot \Big[\int_0^{\gamma_f} h_3(Fe_{pl})\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma \Big]
\end{aligned}
$$

$$
\begin{aligned}
&= -h_3(Fe_{pl})P_3^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\;d\mu\Big]\\
&\quad - h_3(Fe_{pl})\sum_{i=2}^{N_\mu}A_{i,N_\gamma}(t)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\;d\mu\Big]\\
&\quad + \sum_{\ell=1}^{N_\gamma}P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\;d\mu\Big]\\
&\qquad\cdot\Big[\int_0^{\gamma_f}h_3(Fe_{pl})\phi_\ell(\gamma)\phi_k'(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}h_3(Fe_{pl})\phi_\ell(\gamma)\chi_k'(\gamma)\;d\gamma\Big]\\
&\quad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\;d\mu\Big]\\
&\qquad\cdot\Big[\int_0^{\gamma_f}h_3(Fe_{pl})\phi_\ell(\gamma)\phi_k'(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}h_3(Fe_{pl})\phi_\ell(\gamma)\chi_k'(\gamma)\;d\gamma\Big].
\end{aligned}
\tag{31}
$$

6.1.6 States Vectors and Linear ODEs

In order to construct a linear system of ODEs, we reassemble rows 2 through N_μ of the coefficient array $A(t)$ to create a vector. Specifically, the rows of $A(t)$ are converted to columns and stacked on top of one another to create the states vector $x(t)$. Similarly, we reassemble rows 2 through N_μ of $\dot{A}(t)$ to create the vector $\dot{x}(t)$. Thus,

$$
x(t)=\begin{bmatrix}
A_{2,1}\\ A_{2,2}\\ \vdots\\ A_{2,N_\gamma}\\ \hline
A_{3,1}\\ A_{3,2}\\ \vdots\\ A_{3,N_\gamma}\\ \hline
\vdots\\ \hline
A_{N_\mu,1}\\ A_{N_\mu,2}\\ \vdots\\ A_{N_\mu,N_\gamma}
\end{bmatrix}
\qquad\text{and}\qquad
\dot{x}(t)=\begin{bmatrix}
\dot{A}_{2,1}\\ \dot{A}_{2,2}\\ \vdots\\ \dot{A}_{2,N_\gamma}\\ \hline
\dot{A}_{3,1}\\ \dot{A}_{3,2}\\ \vdots\\ \dot{A}_{3,N_\gamma}\\ \hline
\vdots\\ \hline
\dot{A}_{N_\mu,1}\\ \dot{A}_{N_\mu,2}\\ \vdots\\ \dot{A}_{N_\mu,N_\gamma}
\end{bmatrix}.
\tag{32}
$$

Note that x and $\dot{x}$ both have length $n=(N_\mu-1)N_\gamma$.

Our goal is to write a linear system of ODEs of the form

$$
M\dot{x}=Kx+b,
\tag{33}
$$

where $M,K\in\mathbb{R}^{n\times n}$ and $x,\dot{x},b\in\mathbb{R}^n$. As we shall see, the matrices M and K will have block structures. Each of these matrices will be made up of $(N_\mu-1)\times(N_\mu-1)$ blocks, and each block will be an $N_\gamma\times N_\gamma$ matrix.

6.1.7 Mass Matrix

The matrix M, which is called the mass matrix, will be constructed as

$$M = [M_1 + \omega_\mu M_2] \cdot * [M_3 + \omega_\gamma M_4],$$

where "$\cdot *$" denotes element-wise multiplication and the matrices M_1 through M_4 are defined based on the the four integrals in the last term of (27). The matrix M_1 consists of $(N_\mu - 1) \times (N_\mu - 1)$ blocks, each of which is an $N_\gamma \times N_\gamma$ matrix. We will denote these blocks $B^{(1)}_{ji}$. Also, in the definitions that follow, we let any boldface number represent a matrix with that number in every position. Then,

$$M_1 = \begin{bmatrix} B^{(1)}_{1,1} & B^{(1)}_{1,2} & \cdots & B^{(1)}_{1,N_{\mu-1}} \\ B^{(1)}_{2,1} & B^{(1)}_{2,2} & \cdots & B^{(1)}_{2,N_{\mu-1}} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(1)}_{N_{\mu-1},1} & B^{(1)}_{N_{\mu-1},2} & \cdots & B^{(1)}_{N_{\mu-1},N_{\mu-1}} \end{bmatrix},$$

where

$$B^{(1)}_{j-1,i-1} = \left[\int_0^{\mu_f} \phi_i(\mu)\phi_j(\mu)\, d\mu \right] \cdot \mathbf{1} = \begin{cases} \frac{h_\mu}{6} \cdot \mathbf{4} & \text{if} \quad i = j \quad \text{and} \quad i \neq N_\mu \\ \frac{h_\mu}{6} \cdot \mathbf{2} & \text{if} \quad i = j = N_\mu \\ \frac{h_\mu}{6} \cdot \mathbf{1} & \text{if} \quad |i - j| = 1 \\ \mathbf{0} & \text{otherwise} \end{cases}$$

for $i, j \in \{2, \ldots, N_\mu\}$. The matrix M_1 can be written more simply as

$$M_1 = \frac{h_\mu}{6} \begin{bmatrix} \mathbf{4} & \mathbf{1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{1} & \mathbf{4} & \mathbf{1} & \ddots & \vdots \\ \mathbf{0} & \mathbf{1} & \ddots & \ddots & \mathbf{0} \\ \vdots & \ddots & \ddots & \mathbf{4} & \mathbf{1} \\ \mathbf{0} & \cdots & \mathbf{0} & \mathbf{1} & \mathbf{2} \end{bmatrix}.$$

Following the same convention for boldface numbers, we can define

$$M_2 = \begin{bmatrix} B^{(2)}_{1,1} & B^{(2)}_{1,2} & \cdots & B^{(2)}_{1,N_{\mu-1}} \\ B^{(2)}_{2,1} & B^{(2)}_{2,2} & \cdots & B^{(2)}_{2,N_{\mu-1}} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(2)}_{N_{\mu-1},1} & B^{(2)}_{N_{\mu-1},2} & \cdots & B^{(2)}_{N_{\mu-1},N_{\mu-1}} \end{bmatrix},$$

where now

$$B^{(2)}_{j-1,i-1} = \left[\int_0^{\mu_f} \phi_i(\mu)\chi_j(\mu)\, d\mu \right] \cdot \mathbf{1} = \begin{cases} \mathbf{0} & \text{if} \quad i = j \quad \text{and} \quad i \neq N_\mu \\ \frac{h_\mu}{12} \cdot \mathbf{1} & \text{if} \quad i = j = N_\mu \\ -\frac{h_\mu}{12} \cdot \mathbf{1} & \text{if} \quad i - j = 1 \\ \frac{h_\mu}{12} \cdot \mathbf{1} & \text{if} \quad j - i = 1 \\ \mathbf{0} & \text{otherwise} \end{cases}$$

for $i, j \in \{2, \ldots, N_\mu\}$. Thus M_2 can be written

$$M_2 = \frac{h_\mu}{12} \begin{bmatrix} \mathbf{0} & \mathbf{-1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{1} & \mathbf{0} & \mathbf{-1} & \ddots & \vdots \\ \mathbf{0} & \mathbf{1} & \ddots & \ddots & \mathbf{0} \\ \vdots & \ddots & \ddots & \mathbf{0} & \mathbf{-1} \\ \mathbf{0} & \cdots & \mathbf{0} & \mathbf{1} & \mathbf{1} \end{bmatrix}.$$

The matrix M_3 is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(3)}$. We define

$$M_3 = \begin{bmatrix} B^{(3)} & B^{(3)} & \cdots & B^{(3)} \\ B^{(3)} & B^{(3)} & \cdots & B^{(3)} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(3)} & B^{(3)} & \cdots & B^{(3)} \end{bmatrix},$$

where $B^{(3)} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(3)}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\, d\gamma$$

so that

$$B^{(3)} = \frac{h_\gamma}{6} \begin{bmatrix} 2 & 1 & 0 & \cdots & 0 \\ 1 & 4 & 1 & \ddots & \vdots \\ 0 & 1 & \ddots & \ddots & 0 \\ \vdots & \ddots & \ddots & 4 & 1 \\ 0 & \cdots & 0 & 1 & 2 \end{bmatrix}.$$

The matrix M_4 is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(4)}$. We define

$$M_4 = \begin{bmatrix} B^{(4)} & B^{(4)} & \cdots & B^{(4)} \\ B^{(4)} & B^{(4)} & \cdots & B^{(4)} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(4)} & B^{(4)} & \cdots & B^{(4)} \end{bmatrix},$$

where $B^{(4)} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(4)}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\, d\gamma$$

so that

$$B^{(4)} = \frac{h_\gamma}{12} \begin{bmatrix} -1 & -1 & 0 & \cdots & 0 \\ 1 & 0 & -1 & \ddots & \vdots \\ 0 & 1 & \ddots & \ddots & 0 \\ \vdots & \ddots & \ddots & 0 & -1 \\ 0 & \cdots & 0 & 1 & 1 \end{bmatrix}.$$

6.1.8 Stiffness Matrix

The matrix K, which is called the stiffness matrix, will be constructed as

$$K = K^{\mathrm{I}} + K^{\mathrm{II}} + K^{\mathrm{III}} + K^{\mathrm{IV}},$$

where components I though IV are determined by contributions from equations (28) through (31), respectively.

The first component of the stiffness matrix is

$$K^{\mathrm{I}} = 2\beta_3 \left[K_1^{\mathrm{I}} + \omega_\mu K_2^{\mathrm{I}}\right] \cdot * \left[K_3^{\mathrm{I}} + \omega_\gamma K_4^{\mathrm{I}}\right],$$

where "$\cdot *$" denotes element-wise multiplication and the matrices K_1^{I} through K_4^{I} are defined based on the four integrals in the last term of (28). The matrix K_1^{I} consists of $(N_\mu - 1) \times (N_\mu - 1)$ blocks which we denote $B_{ji}^{(\mathrm{I1})}$ (where each $B_{ji}^{(\mathrm{I1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$), so

$$K_1^{\mathrm{I}} = \begin{bmatrix} B_{1,1}^{(\mathrm{I1})} & B_{1,2}^{(\mathrm{I1})} & \cdots & B_{1,N_{\mu-1}}^{(\mathrm{I1})} \\ B_{2,1}^{(\mathrm{I1})} & B_{2,2}^{(\mathrm{I1})} & \cdots & B_{2,N_{\mu-1}}^{(\mathrm{I1})} \\ \vdots & \vdots & \ddots & \vdots \\ B_{N_{\mu-1},1}^{(\mathrm{I1})} & B_{N_{\mu-1},2}^{(\mathrm{I1})} & \cdots & B_{N_{\mu-1},N_{\mu-1}}^{(\mathrm{I1})} \end{bmatrix},$$

where

$$B_{j-1,i-1}^{(\mathrm{I1})} = \left[\int_0^{\mu_f} \phi_i(\mu)\phi_j(\mu)\, d\mu\right] \cdot \mathbf{1}$$

for $i, j \in \{2, \ldots, N_\mu\}$. Note that $B_{ji}^{(\mathrm{I1})} = B_{ji}^{(1)}$, so $K_1^{\mathrm{I}} = M_1$.

The matrix K_2^{I} has the same form as K_1^{I} except that the blocks are given by

$$B_{j-1,i-1}^{(\mathrm{I2})} = \left[\int_0^{\mu_f} \phi_i(\mu)\chi_j(\mu)\, d\mu\right] \cdot \mathbf{1} = B_{j-1,i-1}^{(2)}$$

for $i, j \in \{2, \ldots, N_\mu\}$. Thus, $K_2^{\mathrm{I}} = M_2$.

The matrix K_3^{I} is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(\mathrm{I3})}$. We define

$$K_3^{\mathrm{I}} = \begin{bmatrix} B^{(\mathrm{I3})} & B^{(\mathrm{I3})} & \cdots & B^{(\mathrm{I3})} \\ B^{(\mathrm{I3})} & B^{(\mathrm{I3})} & \cdots & B^{(\mathrm{I3})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{I3})} & B^{(\mathrm{I3})} & \cdots & B^{(\mathrm{I3})} \end{bmatrix},$$

where $B^{(\mathrm{I3})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(\mathrm{I3})}]_{k\ell} = \int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\phi_k(\gamma)\, d\gamma$$

so that

$$B^{(\mathrm{I3})} = \frac{h_\gamma}{24}\begin{bmatrix} 5 & 6 & 1 & 0 & 0 & \cdots & \cdots & \cdots & \cdots & \cdots & 0 \\ 1 & 6 & 10 & 6 & 1 & 0 & 0 & \cdots & \cdots & \cdots & 0 \\ 0 & 0 & 1 & 6 & 10 & 6 & 1 & 0 & 0 & \cdots & 0 \\ \vdots & & & \ddots & \ddots & \ddots & \ddots & \ddots & & & \vdots \\ 0 & \cdots & 0 & 0 & 1 & 6 & 10 & 6 & 1 & 0 & 0 \\ 0 & \cdots & \cdots & \cdots & 0 & 0 & 1 & 6 & 10 & 6 & 1 \\ 0 & \cdots & \cdots & \cdots & \cdots & \cdots & 0 & 0 & 1 & 6 & 5 \\ 0 & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & 0 \\ \vdots & & & & & & & & & & \vdots \\ 0 & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & 0 \end{bmatrix} \begin{matrix} \leftarrow (k=1) \\ \\ \\ \\ \\ \\ \leftarrow \left(k = \frac{N_\gamma+1}{2}\right) \\ \\ \\ \leftarrow (k = N_\gamma) \end{matrix}$$

Note that the upper half of this matrix is *quasi*-diagonal, and that only the upper half contains nonzero entries.

The matrix K_4^{I} is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(\mathrm{I4})}$. We define

$$K_4^{\mathrm{I}} = \begin{bmatrix} B^{(\mathrm{I4})} & B^{(\mathrm{I4})} & \cdots & B^{(\mathrm{I4})} \\ B^{(\mathrm{I4})} & B^{(\mathrm{I4})} & \cdots & B^{(\mathrm{I4})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{I4})} & B^{(\mathrm{I4})} & \cdots & B^{(\mathrm{I4})} \end{bmatrix},$$

where $B^{(\mathrm{I4})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(\mathrm{I4})}]_{k\ell} = \int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\chi_k(\gamma)\, d\gamma$$

so that

$$B^{(\mathrm{I4})} = \frac{h_\gamma}{96}\begin{bmatrix} -3 & -10 & -3 & 0 & 0 & \cdots & \cdots & \cdots & \cdots & \cdots & 0 \\ 3 & 10 & 0 & -10 & -3 & 0 & 0 & \cdots & \cdots & \cdots & 0 \\ 0 & 0 & 3 & 10 & 0 & -10 & -3 & 0 & 0 & \cdots & 0 \\ \vdots & & & \ddots & \ddots & \ddots & \ddots & \ddots & & & \vdots \\ 0 & \cdots & 0 & 0 & 3 & 10 & 0 & -10 & -3 & 0 & 0 \\ 0 & \cdots & \cdots & \cdots & 0 & 0 & 3 & 10 & 0 & -10 & -3 \\ 0 & \cdots & \cdots & \cdots & \cdots & \cdots & 0 & 0 & 3 & 10 & 3 \\ 0 & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & 0 \\ \vdots & & & & & & & & & & \vdots \\ 0 & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & 0 \end{bmatrix} \begin{matrix} \leftarrow (k=1) \\ \\ \\ \\ \\ \\ \leftarrow \left(k = \frac{N_\gamma+1}{2}\right) \\ \\ \\ \leftarrow (k = N_\gamma) \end{matrix}$$

Once again the upper half of this matrix is *quasi*-diagonal, and only the upper half contains nonzero entries.

The second component of the stiffness matrix is

$$K^{\mathrm{II}} = -\left[K_1^{\mathrm{II}} + \omega_\mu K_2^{\mathrm{II}}\right] \cdot * \left[K_3^{\mathrm{II}} + \omega_\gamma K_4^{\mathrm{II}}\right],$$

where "$\cdot *$" denotes element-wise multiplication and the matrices K_1^{II} through K_4^{II} are defined based on the four integrals in the last term of (29). The matrix K_1^{II} consists of $(N_\mu - 1) \times (N_\mu - 1)$ blocks

which we denote $B_{ji}^{(\mathrm{II1})}$ (where each $B_{ji}^{(\mathrm{II1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$), so

$$K_1^{\mathrm{II}} = \begin{bmatrix} B_{1,1}^{(\mathrm{II1})} & B_{1,2}^{(\mathrm{II1})} & \cdots & B_{1,N_{\mu-1}}^{(\mathrm{II1})} \\ B_{2,1}^{(\mathrm{II1})} & B_{2,2}^{(\mathrm{II1})} & \cdots & B_{2,N_{\mu-1}}^{(\mathrm{II1})} \\ \vdots & \vdots & \ddots & \vdots \\ B_{N_{\mu-1},1}^{(\mathrm{II1})} & B_{N_{\mu-1},2}^{(\mathrm{II1})} & \cdots & B_{N_{\mu-1},N_{\mu-1}}^{(\mathrm{II1})} \end{bmatrix},$$

where

$$B_{j-1,i-1}^{(\mathrm{II1})} = \left[\int_0^{\mu_f} \Big(\beta_3 + \delta_3(\mu, EPO) \Big) \phi_i(\mu) \phi_j(\mu) \, d\mu \right] \cdot \mathbf{1}$$

for $i, j \in \{2, \ldots, N_\mu\}$. The variable EPO is time-dependent, so this subcomponent of K^{II} will have to be recomputed at each time step. If we let

$$f(\mu) = \beta_3 + \delta_3(\mu, EPO_{\mathrm{curr}}), \tag{34}$$

where EPO_{curr} is the current EPO level, and then evaluate this function at the nodes we used to partition $[0, \mu_f]$, we can approximate f using a piecewise linear interpolation. If we let $f_k = f(\mu_k)$, then we can approximate the integral defining $B_{j-1,i-1}^{(\mathrm{II1})}$ as

$$\int_0^{\mu_f} f(\mu) \phi_i(\mu) \phi_j(\mu) \, d\mu = \begin{cases} \frac{h_\mu}{12} \left(f_{i-1} + 6 f_i + f_{i+1} \right) & \text{if} \quad i = j \quad \text{and} \quad i \neq N_\mu \\ \frac{h_\mu}{12} \left(f_{i-1} + 3 f_i \right) & \text{if} \quad i = j = N_\mu \\ \frac{h_\mu}{12} \left(f_{i-1} + f_i \right) & \text{if} \quad i - j = 1 \\ \frac{h_\mu}{12} \left(f_i + f_{i+1} \right) & \text{if} \quad j - i = 1 \\ 0 & \text{otherwise.} \end{cases}$$

Thus, the matrix K_1^{II} can be written

$$K_1^{\mathrm{II}} = \frac{h_\mu}{12} \begin{bmatrix} (f_1 + 6f_2 + f_3) \, \mathbf{1} & (f_2 + f_3) \, \mathbf{1} & \mathbf{0} & \cdots & \mathbf{0} \\ (f_2 + f_3) \, \mathbf{1} & \ddots & \ddots & \ddots & \vdots \\ \mathbf{0} & \ddots & \ddots & \ddots & \mathbf{0} \\ \vdots & \ddots & (f_{N_\mu - 2} + f_{N_\mu - 1}) \, \mathbf{1} & (f_{N_\mu - 2} + 6 f_{N_\mu - 1} + f_{N_\mu}) \, \mathbf{1} & (f_{N_\mu - 1} + f_{N_\mu}) \, \mathbf{1} \\ \mathbf{0} & \cdots & \mathbf{0} & (f_{N_\mu - 1} + f_{N_\mu}) \, \mathbf{1} & (f_{N_\mu - 1} + 3 f_{N_\mu}) \, \mathbf{1} \end{bmatrix}.$$

The matrix K_2^{II} has the same form as K_1^{II} except that its blocks are given by

$$B_{j-1,i-1}^{(\mathrm{II2})} = \left[\int_0^{\mu_f} \Big(\beta_3 + \delta_3(\mu, EPO) \Big) \phi_i(\mu) \chi_j(\mu) \, d\mu \right] \cdot \mathbf{1}$$

for $i, j \in \{2, \ldots, N_\mu\}$. If we once again let f be the function defined in (34) and let $f_k = f(\mu_k)$, then

we can approximate the integral defining $B^{(\mathrm{II2})}_{j-1,i-1}$ as

$$\int_0^{\mu_f} f(\mu)\phi_i(\mu)\phi_j(\mu)\,d\mu = \begin{cases} \frac{h_\mu}{60}\left(2f_{i-1} - 2f_{i+1}\right) & \text{if} \quad i = j \quad \text{and} \quad i \neq N_\mu \\ \frac{h_\mu}{60}\left(2f_{i-1} + 3f_i\right) & \text{if} \quad i = j = N_\mu \\ \frac{h_\mu}{60}\left(-2f_{i-1} - 3f_i\right) & \text{if} \quad i - j = 1 \\ \frac{h_\mu}{60}\left(-2f_i + 7f_{i+1}\right) & \text{if} \quad j - i = 1 \text{ and } j < N_\mu \\ \frac{h_\mu}{60}\left(3f_i + 2f_{i+1}\right) & \text{if} \quad j - i = 1 \text{ and } j = N_\mu \\ 0 & \text{otherwise.} \end{cases}$$

Thus, the matrix K_2^{II} can be written

$$K_2^{\mathrm{II}} = \frac{h_\mu}{60}\begin{bmatrix} (2f_1 - 2f_3)\,\mathbf{1} & (-2f_2 - 3f_3)\,\mathbf{1} & \mathbf{0} & \cdots & \mathbf{0} \\ (-2f_2 + 7f_3)\,\mathbf{1} & \ddots & \ddots & \ddots & \vdots \\ \mathbf{0} & \ddots & \ddots & \ddots & \mathbf{0} \\ \vdots & \ddots & (-2f_{N_\mu-2} + 7f_{N_\mu-1})\,\mathbf{1} & (2f_{N_\mu-2} - 2f_{N_\mu})\,\mathbf{1} & (-2f_{N_\mu-1} - 3f_{N_\mu})\,\mathbf{1} \\ \mathbf{0} & \cdots & \mathbf{0} & (3f_{N_\mu-1} + 2f_{N_\mu})\,\mathbf{1} & (2f_{N_\mu-1} + 3f_{N_\mu})\,\mathbf{1} \end{bmatrix}.$$

The matrix K_3^{II} is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(\mathrm{II3})}$. We define

$$K_3^{\mathrm{II}} = \begin{bmatrix} B^{(\mathrm{II3})} & B^{(\mathrm{II3})} & \cdots & B^{(\mathrm{II3})} \\ B^{(\mathrm{II3})} & B^{(\mathrm{II3})} & \cdots & B^{(\mathrm{II3})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{II3})} & B^{(\mathrm{II3})} & \cdots & B^{(\mathrm{II3})} \end{bmatrix},$$

where $B^{(\mathrm{II3})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(\mathrm{II3})}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\,d\gamma = [B^{(3)}]_{k\ell}.$$

Therefore, $K_3^{\mathrm{II}} = M_3$.

The matrix K_4^{II} has the same form as K_3^{II} except that the block matrix $B^{(\mathrm{II4})}$ has entries given by

$$[B^{(\mathrm{II4})}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\,d\gamma = [B^{(4)}]_{k\ell}.$$

Therefore, $K_4^{\mathrm{II}} = M_4$.

The third component of the stiffness matrix is

$$K^{\mathrm{III}} = \rho_3\left[K_1^{\mathrm{III}} + \omega_\mu K_2^{\mathrm{III}}\right] \cdot * \left[K_3^{\mathrm{III}} + \omega_\gamma K_4^{\mathrm{III}}\right] - \rho_3 K_5^{\mathrm{III}},$$

where "$\cdot *$" denotes element-wise multiplication, the matrices K_1^{III} through K_4^{III} are defined based on the four integrals in the last term of (30), and K_5^{III} is defined based on the integrals in the first term of (30).

The matrix K_1^{III} consists of $(N_\mu - 1) \times (N_\mu - 1)$ blocks which we denote $B_{ji}^{(\mathrm{III1})}$ (where each $B_{ji}^{(\mathrm{III1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$), so

$$K_1^{\mathrm{III}} = \begin{bmatrix} B_{1,1}^{(\mathrm{III1})} & B_{1,2}^{(\mathrm{III1})} & \cdots & B_{1,N_{\mu-1}}^{(\mathrm{III1})} \\ B_{2,1}^{(\mathrm{III1})} & B_{2,2}^{(\mathrm{III1})} & \cdots & B_{2,N_{\mu-1}}^{(\mathrm{III1})} \\ \vdots & \vdots & \ddots & \vdots \\ B_{N_{\mu-1},1}^{(\mathrm{III1})} & B_{N_{\mu-1},2}^{(\mathrm{III1})} & \cdots & B_{N_{\mu-1},N_{\mu-1}}^{(\mathrm{III1})} \end{bmatrix},$$

where

$$B_{j-1,i-1}^{(\mathrm{III1})} = \left[\int_0^{\mu_f} \phi_i(\mu) \phi_j'(\mu) \, d\mu \right] \cdot \mathbf{1} = \begin{cases} \mathbf{0} & \text{if} \quad i = j \quad \text{and} \quad i \neq N_\mu \\ \frac{1}{2} \cdot \mathbf{1} & \text{if} \quad i = j = N_\mu \\ -\frac{1}{2} \cdot \mathbf{1} & \text{if} \quad i - j = 1 \\ \frac{1}{2} \cdot \mathbf{1} & \text{if} \quad j - i = 1 \\ \mathbf{0} & \text{otherwise} \end{cases}$$

for $i, j \in \{2, \ldots, N_\mu\}$. The matrix K_1^{III} can be written more simply as

$$K_1^{\mathrm{III}} = \frac{1}{2} \begin{bmatrix} \mathbf{0} & -\mathbf{1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{1} & \mathbf{0} & -\mathbf{1} & \ddots & \vdots \\ \mathbf{0} & \mathbf{1} & \ddots & \ddots & \mathbf{0} \\ \vdots & \ddots & \ddots & \mathbf{0} & -\mathbf{1} \\ \mathbf{0} & \cdots & \mathbf{0} & \mathbf{1} & \mathbf{1} \end{bmatrix}.$$

The matrix K_2^{III} has the same form as K_1^{III} except that its blocks are given by

$$B_{j-1,i-1}^{(\mathrm{III2})} = \left[\int_0^{\mu_f} \phi_i(\mu) \chi_j'(\mu) \, d\mu \right] \cdot \mathbf{1} = \begin{cases} -\frac{1}{6} \cdot \mathbf{2} & \text{if} \quad i = j \quad \text{and} \quad i \neq N_\mu \\ -\frac{1}{6} \cdot \mathbf{1} & \text{if} \quad i = j = N_\mu \\ \frac{1}{6} \cdot \mathbf{1} & \text{if} \quad |i - j| = 1 \\ \mathbf{0} & \text{otherwise} \end{cases}$$

for $i, j \in \{2, \ldots, N_\mu\}$. The matrix K_2^{III} can be written more simply as

$$K_2^{\mathrm{III}} = \frac{1}{6} \begin{bmatrix} -\mathbf{2} & \mathbf{1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{1} & -\mathbf{2} & \mathbf{1} & \ddots & \vdots \\ \mathbf{0} & \mathbf{1} & \ddots & \ddots & \mathbf{0} \\ \vdots & \ddots & \ddots & -\mathbf{2} & \mathbf{1} \\ \mathbf{0} & \cdots & \mathbf{0} & \mathbf{1} & -\mathbf{1} \end{bmatrix}.$$

The matrix K_3^{III} is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(\mathrm{III3})}$. We define

$$K_3^{\mathrm{III}} = \begin{bmatrix} B^{(\mathrm{III3})} & B^{(\mathrm{III3})} & \cdots & B^{(\mathrm{III3})} \\ B^{(\mathrm{III3})} & B^{(\mathrm{III3})} & \cdots & B^{(\mathrm{III3})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{III3})} & B^{(\mathrm{III3})} & \cdots & B^{(\mathrm{III3})} \end{bmatrix},$$

where $B^{(\mathrm{III}3)} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(\mathrm{III}3)}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma = [B^{(3)}]_{k\ell}.$$

Therefore, $K_3^{\mathrm{III}} = M_3$.

The matrix K_4^{III} has the same form as K_3^{III} except that the block matrix $B^{(\mathrm{III}4)}$ has entries given by

$$[B^{(\mathrm{III}4)}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma = [B^{(4)}]_{k\ell}.$$

Therefore, $K_4^{\mathrm{III}} = M_4$.

The matrix K_5^{III} consists of $(N_\mu - 1) \times (N_\mu - 1)$ blocks which we denote $B_{ji}^{(\mathrm{III}5)}$, so

$$K_5^{\mathrm{III}} = \begin{bmatrix} B_{1,1}^{(\mathrm{III}5)} & B_{1,2}^{(\mathrm{III}5)} & \cdots & B_{1,N_{\mu-1}}^{(\mathrm{III}5)} \\ B_{2,1}^{(\mathrm{III}5)} & B_{2,2}^{(\mathrm{III}5)} & \cdots & B_{2,N_{\mu-1}}^{(\mathrm{III}5)} \\ \vdots & \vdots & \ddots & \vdots \\ B_{N_{\mu-1},1}^{(\mathrm{III}5)} & B_{N_{\mu-1},2}^{(\mathrm{III}5)} & \cdots & B_{N_{\mu-1},N_{\mu-1}}^{(\mathrm{III}5)} \end{bmatrix}.$$

Note that the term responsible for generating this matrix is

$$\sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_j(\mu = \mu_f) \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right].$$

Because the only $A_{i,\ell}(t)$ terms that are present are those for which $i = N_\mu$, and because $\phi_j(\mu = \mu_f)$ is only nonzero when $j = N_\mu$, the only nonzero block in this matrix is the block corresponding to $i = j = N_\mu$ (the block in the lower right-hand corner of the matrix.) Thus,

$$K_5^{\mathrm{III}} = \begin{bmatrix} \mathbf{0} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \ddots & \ddots & \vdots \\ \vdots & \ddots & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \cdots & \mathbf{0} & B^{(\mathrm{III}5)} \end{bmatrix},$$

where $B^{(\mathrm{III}5)} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(\mathrm{III}5)}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma.$$

The matrix $B^{(\mathrm{III}5)}$, then, is precisely the lower right-hand block (or any other block, since all the blocks are identical) in the matrix $M_3 + \omega_\gamma M_4$; i.e.,

$$\begin{aligned} B^{(\mathrm{III}5)} &= [M_3 + \omega_\gamma M_4](\text{end } - N_\gamma + 1 : \text{end},\ \text{end } - N_\gamma + 1 : \text{end}) \\ &= [M_3 + \omega_\gamma M_4](1 : N_\gamma, 1 : N_\gamma). \end{aligned}$$

Here, we have used the notation $[M](a : b, c : d)$ to indicate the matrix consisting of rows a through b and columns c through d of the parent matrix M. In the context of this notation, we use the word "end" to indicate the final row or column of the matrix.

The fourth component of the stiffness matrix is

$$K^{\mathrm{IV}} = \left[K_1^{\mathrm{IV}} + \omega_\mu K_2^{\mathrm{IV}}\right] \cdot * \, h_3(Fe_{pl}) \left[K_3^{\mathrm{IV}} + \omega_\gamma K_4^{\mathrm{IV}}\right] - h_3(Fe_{pl}) K_5^{\mathrm{IV}},$$

where "$\cdot *$" denotes element-wise multiplication, the matrices K_1^{IV} through K_4^{IV} are defined based on the four integrals in the last term of (31), and K_5^{IV} is defined based on the integrals in the second term of (31).

The matrix K_1^{IV} consists of $(N_\mu - 1) \times (N_\mu - 1)$ blocks which we denote $B_{ji}^{(\mathrm{IV1})}$ (where each $B_{ji}^{(\mathrm{IV1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$), so

$$K_1^{\mathrm{IV}} = \begin{bmatrix} B_{1,1}^{(\mathrm{IV1})} & B_{1,2}^{(\mathrm{IV1})} & \cdots & B_{1,N_{\mu-1}}^{(\mathrm{IV1})} \\ B_{2,1}^{(\mathrm{IV1})} & B_{2,2}^{(\mathrm{IV1})} & \cdots & B_{2,N_{\mu-1}}^{(\mathrm{IV1})} \\ \vdots & \vdots & \ddots & \vdots \\ B_{N_{\mu-1},1}^{(\mathrm{IV1})} & B_{N_{\mu-1},2}^{(\mathrm{IV1})} & \cdots & B_{N_{\mu-1},N_{\mu-1}}^{(\mathrm{IV1})} \end{bmatrix},$$

where

$$B_{j-1,i-1}^{(\mathrm{IV1})} = \left[\int_0^{\mu_f} \phi_i(\mu)\phi_j(\mu)\, d\mu\right] \cdot \mathbf{1}$$

for $i, j \in \{2, \ldots, N_\mu\}$. Note that $B_{ji}^{(\mathrm{IV1})} = B_{ji}^{(1)}$, so $K_1^{\mathrm{IV}} = M_1$.

The matrix K_2^{IV} has the same form as K_1^{IV} except that the blocks are given by

$$B_{j-1,i-1}^{(\mathrm{IV2})} = \left[\int_0^{\mu_f} \phi_i(\mu)\chi_j(\mu)\, d\mu\right] \cdot \mathbf{1} = B_{j-1,i-1}^{(2)}$$

for $i, j \in \{2, \ldots, N_\mu\}$. Thus $K_2^{\mathrm{IV}} = M_2$.

The matrix K_3^{IV} is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(\mathrm{IV3})}$. We define

$$K_3^{\mathrm{IV}} = \begin{bmatrix} B^{(\mathrm{IV3})} & B^{(\mathrm{IV3})} & \cdots & B^{(\mathrm{IV3})} \\ B^{(\mathrm{IV3})} & B^{(\mathrm{IV3})} & \cdots & B^{(\mathrm{IV3})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{IV3})} & B^{(\mathrm{IV3})} & \cdots & B^{(\mathrm{IV3})} \end{bmatrix},$$

where $B^{(\mathrm{IV3})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(\mathrm{IV3})}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k'(\gamma)\, d\gamma$$

so that

$$B^{(\mathrm{IV3})} = \frac{1}{2} \begin{bmatrix} -1 & -1 & 0 & \cdots & 0 \\ 1 & 0 & -1 & \ddots & \vdots \\ 0 & 1 & \ddots & \ddots & 0 \\ \vdots & \ddots & \ddots & 0 & -1 \\ 0 & \cdots & 0 & 1 & 1 \end{bmatrix}.$$

The matrix K_4^{IV} has the same form as K_3^{IV} except that the block matrix $B^{(\mathrm{IV4})}$ has entries given by

$$[B^{(\mathrm{IV4})}]_{k\ell} = \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma$$

so that

$$B^{(\mathrm{IV4})} = \frac{1}{6}\begin{bmatrix} -1 & 1 & 0 & \cdots & 0 \\ 1 & -2 & 1 & \ddots & \vdots \\ 0 & 1 & \ddots & \ddots & 0 \\ \vdots & \ddots & \ddots & -2 & 1 \\ 0 & \cdots & 0 & 1 & -1 \end{bmatrix}.$$

The matrix K_5^{IV} consists of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks which we denote $B^{(\mathrm{IV5})}$, so

$$K_5^{\mathrm{IV}} = \begin{bmatrix} B^{(\mathrm{IV5})} & B^{(\mathrm{IV5})} & \cdots & B^{(\mathrm{IV5})} \\ B^{(\mathrm{IV5})} & B^{(\mathrm{IV5})} & \cdots & B^{(\mathrm{IV5})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{IV5})} & B^{(\mathrm{IV5})} & \cdots & B^{(\mathrm{IV5})} \end{bmatrix}.$$

Note that the term responsible for generating this matrix is

$$\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_k(\gamma = \gamma_f) \cdot \Big[\int_0^{\mu_f} \phi_i(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_i(\mu)\chi_j(\mu)\ d\mu \Big].$$

Because the only $A_{i,\ell}(t)$ terms that are present are those for which $\ell = N_\gamma$, and because $\phi_k(\gamma = \gamma_f)$ is only nonzero when $k = N_\gamma$, the only nonzero elements in this matrix are those corresponding to $k = \ell = N_\gamma$ (the lower right-hand element of each block.) Thus, if we define $D \in \mathbb{R}^{N_\gamma \times N_\gamma}$ as

$$D = \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & \vdots \\ \vdots & \ddots & 0 & 0 \\ 0 & \cdots & 0 & 1 \end{bmatrix},$$

then

$$K_5^{\mathrm{IV}} = \begin{bmatrix} D & D & \cdots & D \\ D & D & \cdots & D \\ \vdots & \vdots & \ddots & \vdots \\ D & D & \cdots & D \end{bmatrix} \cdot * \left[M_1 + \omega_\mu M_2 \right],$$

where "$\cdot *$" denotes element-wise multiplication.

6.1.9 The Boundary Conditions Vector

The only item in (33) which we have yet to describe is the vector b, which incorporates all contributions from the boundary conditions stated in (23). This vector will be constructed as

$$b = b^{\mathrm{I}} + b^{\mathrm{II}} + b^{\mathrm{III}} + b^{\mathrm{IV}} + b^{\mathrm{V}},$$

where components I though V are determined by contributions from equations (27) through (31), respectively.

The vector $b^{\mathrm{I}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ is generated by the term

$$-\sum_{\ell=1}^{N_\gamma} \frac{\partial}{\partial t} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu \right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right]$$

in (27), where we have changed the sign to place the vector on the right-hand side of (33). This vector has the same block form as the states vectors described in (32), so $j \in \{2, \ldots, N_\mu\}$ indicates a specific block and $k \in \{1, \ldots, N\gamma\}$ indicates the position within that block. The expression in the first pair of brackets above is only nonzero for $j = 2$, so only entries in the first block of b^{I} are nonzero. Now if we consider the vector $\dot{v} \in \mathbb{R}^{N_\gamma}$ given by $\dot{v}_\ell = \frac{\partial}{\partial t} P_3^{bdy,\mu}(t,\gamma_\ell)$ and define a matrix $C^{(\mathrm{I})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\mathrm{I})}]_{k\ell} = \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right],$$

then

$$b^{\mathrm{I}} = -\left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12} \right) \cdot \begin{bmatrix} C^{(\mathrm{I})}\dot{v} \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N\gamma}$. Revisiting the derivation for the mass matrix components M_3 and M_4, it is clear that

$$C^{(\mathrm{I})} = B^{(3)} + \omega_\gamma B^{(4)}.$$

The vector $b^{\mathrm{II}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ is generated by the term

$$2\beta_3 \sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu \right] \cdot \left[\int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\chi_k(\gamma)\ d\gamma \right]$$

in (28). This vector has the same block form as the states vectors described in (32), so $j \in \{2, \ldots, N_\mu\}$ indicates a specific block and $k \in \{1, \ldots, N\gamma\}$ indicates the position within that block. The expression in the first pair of brackets above is only nonzero for $j = 2$, so only entries in the first block of b^{II} are nonzero. Now if we consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_3^{bdy,\mu}(t,\gamma_\ell)$ and define a matrix $C^{(\mathrm{II})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\mathrm{II})}]_{k\ell} = \left[\int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\frac{\gamma_f}{2}} \phi_\ell(2\gamma)\chi_k(\gamma)\ d\gamma \right],$$

then

$$b^{\mathrm{II}} = 2\beta_3 \cdot \left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12} \right) \cdot \begin{bmatrix} C^{(\mathrm{II})} v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N\gamma}$. Revisiting the derivation for the stiffness matrix components K_3^{I} and K_4^{I}, it is clear that

$$C^{(\mathrm{II})} = B^{(\mathrm{I3})} + \omega_\gamma B^{(\mathrm{I4})}.$$

The vector $b^{\mathrm{III}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ is generated by the term

$$-\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t, \gamma_\ell) \cdot \Bigg[\int_0^{\mu_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big) \phi_1(\mu)\phi_j(\mu)\, d\mu + \omega_\mu \int_0^{\mu_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big) \phi_1(\mu)\chi_j(\mu)\, d\mu \Bigg] \cdot \Bigg[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\, d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\, d\gamma \Bigg]$$

in (29). This vector has the same block form as the states vectors described in (32), so $j \in \{2, \ldots, N_\mu\}$ indicates a specific block and $k \in \{1, \ldots, N\gamma\}$ indicates the position within that block. Since the expressions $\phi_1(\mu)\phi_j(\mu)$ and $\phi_1(\mu)\chi_j(\mu)$ are only nonzero for $j = 2$, only entries in the first block of b^{III} are nonzero. Now, if we consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_3^{bdy,\mu}(t, \gamma_\ell)$ and define a matrix $C^{(\mathrm{III})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\mathrm{III})}]_{k\ell} = \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\, d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\, d\gamma \right],$$

then

$$b^{\mathrm{III}} = -\left[\int_0^{\mu_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big) \phi_1(\mu)\phi_2(\mu)\, d\mu + \omega_\mu \int_0^{\mu_f} \Big(\beta_3 + \delta_3(\mu, EPO)\Big) \phi_1(\mu)\chi_2(\mu)\, d\mu \right] \cdot \begin{bmatrix} C^{(\mathrm{III})} v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N\gamma}$. We note here that $C^{(\mathrm{III})} = C^{(\mathrm{I})}$ and that the quantity in the first pair of brackets is time-dependent because EPO is time-dependent. If we again define f as in (34) and let $f_k = f(\mu_k)$, then we can approximate the integrals within this first pair

of brackets to obtain the simplified expression

$$b^{\mathrm{III}} = -\left(\frac{h_\mu}{12}\left(f_1+f_2\right)+\omega_\mu\frac{h_\mu}{60}\left(-2f_1+7f_2\right)\right)\cdot\begin{bmatrix} C^{(\mathrm{III})}v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix}.$$

The vector $b^{\mathrm{IV}} \in \mathbb{R}^{(N_\mu-1)N_\gamma}$ can be computed as

$$b^{\mathrm{IV}} = b_1^{\mathrm{IV}} + b_2^{\mathrm{IV}},$$

where b_1^{IV} is generated by the term

$$\rho_3\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\cdot\left[\int_0^{\mu_f}\phi_1(\mu)\phi_j'(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j'(\mu)\;d\mu\right]$$
$$\cdot\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right]$$

in (30) and b_2^{IV} is generated by the term

$$\rho_3\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell)\phi_j(\mu=0)\cdot\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right]$$

also in (30). These vectors have the same block form as the states vectors described in (32), so $j \in \{2,\ldots,N_\mu\}$ indicates a specific block and $k \in \{1,\ldots,N\gamma\}$ indicates the position within that block.

Note that $\phi_1(\mu)\phi_j'(\mu)$ and $\phi_1(\mu)\chi_j'(\mu)$ are only nonzero for $j=2$, so only entries in the first block of b_1^{IV} are nonzero. Now if we consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_3^{bdy,\mu}(t,\gamma_\ell)$ and define a matrix $C^{(\mathrm{IV1})} \in \mathbb{R}^{N_\gamma\times N_\gamma}$ with entries given by

$$[C^{(\mathrm{IV1})}]_{k\ell} = \left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right],$$

then

$$b_1^{\mathrm{IV}} = \rho_3\cdot\left(\frac{1}{2}+\frac{1}{6}\omega_\mu\right)\cdot\begin{bmatrix} C^{(\mathrm{IV1})}v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0,\ldots,0)^T \in \mathbb{R}^{N\gamma}$. Note that $C^{(\mathrm{IV1})} = C^{(\mathrm{I})}$. Also, note that $\phi_j(\mu=0)=0$ for all $j \in \{2,\ldots,N_\mu\}$, so $b_2^{\mathrm{IV}} = (0,\ldots,0)^T$. Therefore, $b^{\mathrm{IV}} = b_1^{\mathrm{IV}}$.

The vector $b^{\mathrm{V}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ can be computed as

$$b^{\mathrm{V}} = b_1^{\mathrm{V}} + b_2^{\mathrm{V}},$$

where b_1^{V} is generated by the term

$$\sum_{\ell=1}^{N_\gamma} P_3^{bdy,\mu}(t,\gamma_\ell) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu \Big] \cdot \Big[\int_0^{\gamma_f} h_3(Fe_{pl})\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} h_3(Fe_{pl})\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma \Big]$$

in (31) and b_2^{V} is generated by the term

$$-h_3(Fe_{pl})P_3^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu \Big],$$

also in (31). These vectors have the same block form as the states vectors described in (32), so $j \in \{2,\dots,N_\mu\}$ indicates a specific block and $k \in \{1,\dots,N\gamma\}$ indicates the position within that block.

Note that $\phi_1(\mu)\phi_j(\mu)$ and $\phi_1(\mu)\chi_j(\mu)$ are only nonzero for $j = 2$ and, so only entries in the first block of b_1^{V} are nonzero. If we once again consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_3^{bdy,\mu}(t,\gamma_\ell)$ and define a matrix $C^{(\mathrm{V1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\mathrm{V1})}]_{k\ell} = \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma \right],$$

then

$$b_1^{\mathrm{V}} = \left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12} \right) \cdot h_3(Fe_{pl}) \cdot \begin{bmatrix} C^{(\mathrm{V1})}v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0,\dots,0)^T \in \mathbb{R}^{N^\gamma}$. Revisiting the derivation for the stiffness matrix components K_3^{IV} and K_4^{IV}, it is clear that

$$C^{(\mathrm{VI})} = B^{(\mathrm{IV3})} + \omega_\gamma B^{(\mathrm{IV4})}.$$

For the vector b_2^{V}, note again that the integrals in the brackets are only nonzero for $j = 2$. Also, because $\phi_k(\gamma = \gamma_f)$ is only nonzero when $k = N_\gamma$, the only nonzero element in this vector is the last

element of the first block. In fact,

$$b_2^{\mathrm{V}} = -h_3(Fe_{pl}) \cdot P_3^{bdy,\mu}(t,\gamma_f) \cdot \left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12}\right) \cdot \left[\begin{array}{c} 0 \\ \vdots \\ 0 \\ 1 \\ \hline 0 \\ \vdots \\ 0 \\ \hline \vdots \\ \hline 0 \\ \vdots \\ 0 \end{array}\right].$$

6.1.10 Testing Numerical Solver for Class $\mathbf{P}_3$ PDE

We test the numerical solution technique described above by applying it to a problem with a known solution. That is, we utilize the so-called "method of synthetic solutions". To begin, we append a "forcing term" to the PDE given in (21) to obtain the new PDE

$$\begin{aligned}\frac{\partial}{\partial t}\tilde{P}_3(t,\mu,\gamma) = \chi_{\left[0,\frac{\gamma_f}{2}\right]}(\gamma) 2\beta_3 \tilde{P}_3(t,\mu,2\gamma) - [\beta_3 + \delta_3(\mu, EPO)]\tilde{P}_3(t,\mu,\gamma) - \rho_3 \frac{\partial}{\partial \mu}\tilde{P}_3(t,\mu,\gamma) \\ - \frac{\partial}{\partial \gamma}\left[h_3(Fe_{pl})\tilde{P}_3(t,\mu,\gamma)\right] + f(t,\mu,\gamma). \end{aligned} \tag{35}$$

Next, we select our "known solution" to be

$$\tilde{P}_3(t,\mu,\gamma) = \left(\sin\frac{2\pi t}{3} + 2\right) \cdot \left(\frac{\mu}{\mu_f} + 1\right) \cdot \left(e^{\gamma/\gamma_f} - 1\right).$$

This solution was chosen to have a temporal period of 3 days since the solver can generate solutions for that period in a reasonable amount of time. Solving (35) for $f(t,\mu,\gamma)$ and then substituting in the known solution, we obtain

$$\begin{aligned} f(t,\mu,\gamma) = \frac{\partial}{\partial t}\tilde{P}_3(t,\mu,\gamma) - \chi_{\left[0,\frac{\gamma_f}{2}\right]}(\gamma) 2\beta_3 \tilde{P}_3(t,\mu,2\gamma) + [\beta_3 + \delta_3(\mu, EPO)]\tilde{P}_3(t,\mu,\gamma) \\ + \rho_3 \frac{\partial}{\partial \mu}\tilde{P}_3(t,\mu,\gamma) + h_3(Fe_{pl})\left[\frac{\partial}{\partial \gamma}\tilde{P}_3(t,\mu,\gamma)\right] \end{aligned}$$

$$
\begin{aligned}
f(t,\mu,\gamma) = &\left(\frac{2\pi}{3}\cos\frac{2\pi t}{3}\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right)\\
&-\chi_{\left[0,\frac{\gamma_f}{2}\right]}(\gamma)2\beta_3\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{2\gamma/\gamma_f}-1\right)\\
&+\left[\beta_3+\delta_3(\mu,EPO)\right]\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right)\\
&+\rho_3\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{1}{\mu_f}\right)\left(e^{\gamma/\gamma_f}-1\right)\\
&+h_3(Fe_{pl})\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(\frac{1}{\gamma_f}e^{\gamma/\gamma_f}\right)
\end{aligned}
$$

Now, the weak form for the class P_3 PDE becomes

$$
\begin{aligned}
&\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial t}P_3(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 1]}\\
&\quad=2\beta_3\int_0^{\mu_f}\int_0^{\frac{\gamma_f}{2}}P_3(t,\mu,2\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 2]}\\
&\quad-\int_0^{\mu_f}\int_0^{\gamma_f}\Big(\beta_3+\delta_3(\mu,EPO)\Big)P_3(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 3]}\\
&\quad-\rho_3\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\mu}P_3(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 4]}\\
&\quad-\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\gamma}\Big(h_3(Fe_{pl})P_3(t,\mu,\gamma)\Big)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 5]}\\
&\quad+\int_0^{\mu_f}\int_0^{\gamma_f}f(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Forcing Term].}
\end{aligned}
$$

Thus, the ODE for the row corresponding to each (j,k) in (33) will have an additional "forcing term". These additional terms force the numerical solver to return the desired solution $\tilde{P}_3(t,\mu,\gamma)$. Note that the initial conditions must be set to

$$\tilde{P}_3(0,\mu,\gamma)=\tilde{P}_3^{init}(\mu,\gamma)=2\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right)$$

and the $\mu=0$ boundary conditions must be set to

$$\tilde{P}_3(t,0,\gamma)=\tilde{P}_3^{bdy,\mu}(t,\gamma)=\left(\sin\frac{2\pi t}{3}+2\right)\left(e^{\gamma/\gamma_f}-1\right)$$

when using this validation technique.

6.2 Numerical Solution of Class P_4 PDE

6.2.1 Description of Initial-Value/Boundary-Value problem

The PDE (9) describing cells in class P_4 can be restated as

$$
\begin{aligned}
\frac{\partial}{\partial t}P_4(t,\mu,\gamma) = &-\delta_4(\mu,\gamma)P_4(t,\mu,\gamma)-\rho_4\frac{\partial}{\partial\mu}P_4(t,\mu,\gamma)\\
&-\frac{\partial}{\partial\gamma}\left[h_4(Fe_{pl},\gamma)P_4(t,\mu,\gamma)\right].
\end{aligned}
\tag{36}
$$

Here, we have replaced μ_4 by μ to simplify notation in the sections that follow. This variable μ and the variables N_μ, μ_f, h_μ, and ω_μ described in the following sections are distinct from those used for class P_3.

Using the same notational conventions, the initial condition is given by

$$P_4(0, \mu, \gamma) = P_4^{init}(\mu, \gamma)$$

for $(\mu, \gamma) \in (0, \mu_f] \times [0, \gamma_f]$.

The $\gamma = 0$ boundary condition is given by

$$h_4(Fe_{pl}, 0)P_4(t, \mu, 0) = 0. \tag{37}$$

for $\mu \in [0, \mu_f]$ and the $\mu = 0$ boundary condition is given by

$$P_4(t, 0, \gamma) = P_4^{bdy,\mu}(t, \gamma) = P_3(t, (\mu_3)_f, \gamma), \tag{38}$$

for $\gamma \in [0, \gamma_f]$.

6.2.2 Mesh on "Spatial" Domain

We partition $[0, \mu_f]$ with N_μ equally-spaced nodes $\{0 = \mu_1, \mu_2, \ldots, \mu_{N_\mu} = \mu_f\}$ using a step size

$$h_\mu = \frac{\mu_f}{(N_\mu - 1)}.$$

Similarly, we partition $[0, \gamma_f]$ with N_γ equally-spaced nodes $\{0 = \gamma_1, \gamma_2, \ldots, \gamma_{N_\gamma} = \gamma_f\}$ using a step size

$$h_\gamma = \frac{\gamma_f}{(N_\gamma - 1)}.$$

We ensure that N_γ is odd so that a node exists at $\frac{\gamma_f}{2}$.

By pairing nodes from these two partitions, we can construct a mesh on $[0, \mu_f] \times [0, \gamma_f]$ consisting of the grid points $\big\{(\mu_i, \gamma_\ell) \mid i \in \{1, 2, \ldots, N_\mu\} \text{ and } \ell \in \{1, 2, \ldots, N_\gamma\}\big\}$.

6.2.3 Test Functions

In order to develop the weak formulation of (36), we use test functions of the same form as those that were used for class P_3.

6.2.4 Weak Formulation

We multiply (36) by test functions $\tilde{\phi}_j(\mu)$ and $\tilde{\phi}_k(\gamma)$ and integrate over the entire spatial domain $[0, \mu_f] \times [0, \gamma_f]$ to obtain the weak formulation

$$\begin{aligned}
\int_0^{\mu_f} \int_0^{\gamma_f} \frac{\partial}{\partial t} P_4(t, \mu, \gamma) \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\, d\gamma\, d\mu \quad &\text{[Term 1]} \\
= -\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu, \gamma) P_4(t, \mu, \gamma) \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\, d\gamma\, d\mu \quad &\text{[Term 2]} \\
- \rho_4 \int_0^{\mu_f} \int_0^{\gamma_f} \frac{\partial}{\partial \mu} P_4(t, \mu, \gamma) \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\, d\gamma\, d\mu \quad &\text{[Term 3]} \\
- \int_0^{\mu_f} \int_0^{\gamma_f} \frac{\partial}{\partial \gamma} \Big(h_4(Fe_{pl}, \gamma) P_4(t, \mu, \gamma) \Big) \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\, d\gamma\, d\mu \quad &\text{[Term 4].}
\end{aligned} \tag{39}$$

6.2.5 Numerical Solution

Now, we assume that the approximate solution can be expressed in the form

$$\begin{aligned}
P_4^a(t,\mu,\gamma) &= \sum_{i=1}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\
&= \sum_{\ell=1}^{N_\gamma} P_4(t,\mu_1,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\
&= \sum_{\ell=1}^{N_\gamma} P_4(t,0,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\
&= \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma), \qquad (40)
\end{aligned}$$

where $A_{i,\ell}(t)$ represents the approximate value of $P_4(t,\mu_i,\gamma_\ell)$. As was the case for the numerical solution for P_3, we can visualize the $N_\mu \times N_\gamma$ coefficient matrix $A(t)$ as an array of function values corresponding to a set of points in the region $[0,\mu_f]\times[0,\gamma_f]$. Again, since each entry corresponding to $i=1$ is a known quantity based on the boundary condition (38), this array can be expressed as

$$\begin{array}{c} \\ (i=1) \\ (i=2) \\ \vdots \\ (i=N_\mu) \end{array}
\begin{array}{c}
\begin{array}{cccc} (\ell=1) & (\ell=2) & \cdots & (\ell=N_\gamma) \end{array} \\
\left[\begin{array}{cccc}
P_4^{bdy,\mu}(t,\gamma_1) & P_4^{bdy,\mu}(t,\gamma_2) & \dots & P_4^{bdy,\mu}(t,\gamma_f) \\
A_{2,1}(t) & A_{2,2}(t) & \dots & A_{2,N_\gamma}(t) \\
\vdots & \vdots & & \vdots \\
A_{N_\mu,1}(t) & A_{N_\mu,2}(t) & \cdots & A_{N_\mu,N_\gamma}(t)
\end{array}\right]
\end{array}$$

Differentiating (40) with respect to time, we see that

$$\frac{\partial}{\partial t}P_4^a(t,\mu,\gamma) = \sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma), \qquad (41)$$

where $\dot{A}_{i,\ell}(t)$ represents the approximate value of $\frac{\partial}{\partial t}P_4(t,\mu_i,\gamma_\ell)$ at each grid point of the mesh (except those on the $\mu=0$ boundary). Note that $\frac{\partial}{\partial t}P_4^{bdy,\mu}(t,\gamma_\ell)$ can be computed by taking the time derivative of $P_3(t,(\mu_3)_f,\gamma)$. In practice, a numerical solution P_3^a will be used, so a numerical approximation of this time derivative can be computed.

Our problem now consists of finding $\left\{A_{i,\ell}(t) \mid i\in\{2,3,\dots,N_\mu\} \text{ and } \ell\in\{1,2,\dots,N_\gamma\}\right\}$. We can accomplish this by constructing and solving a system of ODEs consisting of a total of $(N_\mu-1)N_\gamma$ equations. To obtain this system of ODEs, we replace P_4 and $\frac{\partial}{\partial t}P_4$ in (39) by the approximations P_4^a and $\frac{\partial}{\partial t}P_4^a$ described in (40) and (41). For example, Term 1 in (39) becomes

$$\begin{aligned}
&\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial t}P_4^a(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \\
&\quad= \int_0^{\mu_f}\int_0^{\gamma_f}\Big(\sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma)\Big) \\
&\qquad\qquad \cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu
\end{aligned}$$

$$
\begin{aligned}
&= \sum_{\ell=1}^{N_\gamma} \frac{\partial}{\partial t} P_4^{bdy,\mu}(t,\gamma_\ell) \cdot \int_0^{\mu_f} \int_0^{\gamma_f} \phi_1(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} \dot{A}_{i,\ell}(t) \cdot \int_0^{\mu_f} \int_0^{\gamma_f} \phi_i(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&= \sum_{\ell=1}^{N_\gamma} \frac{\partial}{\partial t} P_4^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu\right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} \dot{A}_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu\right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right] \\
&= \sum_{\ell=1}^{N_\gamma} \frac{\partial}{\partial t} P_4^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu\right] \\
&\qquad\qquad \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma\right] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} \dot{A}_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \phi_i(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_i(\mu)\chi_j(\mu)\ d\mu\right] \\
&\qquad\qquad \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma\right]. \qquad (42)
\end{aligned}
$$

Substituting P_4^a into Term 2 in (39), we obtain

$$
\begin{aligned}
&-\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma) P_4^a(t,\mu,\gamma) \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = -\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma) \cdot \Big(\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell) \cdot \phi_1(\mu) \cdot \phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \phi_i(\mu) \cdot \phi_\ell(\gamma)\Big) \\
&\qquad\qquad \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = -\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell) \int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\qquad - \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_i(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = -\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j(\mu) \cdot \left[\int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right]\ d\mu\right] \\
&\qquad - \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j(\mu) \cdot \left[\int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right]\ d\mu\right]
\end{aligned}
$$

$$
\begin{aligned}
&= -\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\int_0^{\mu_f}\Bigg[\Big(\phi_1(\mu)\phi_j(\mu)+\omega_\mu\phi_1(\mu)\chi_j(\mu)\Big)\\
&\qquad\qquad\cdot\int_0^{\gamma_f}\Big(\delta_4(\mu,\gamma)\phi_\ell(\gamma)\phi_k(\gamma)+\omega_\gamma\delta_4(\mu,\gamma)\phi_\ell(\gamma)\chi_k(\gamma)\Big)\,d\gamma\Bigg]\,d\mu\\
&\quad-\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\int_0^{\mu_f}\Bigg[\Big(\phi_i(\mu)\phi_j(\mu)+\omega_\mu\phi_i(\mu)\chi_j(\mu)\Big)\\
&\qquad\qquad\cdot\int_0^{\gamma_f}\Big(\delta_4(\mu,\gamma)\phi_\ell(\gamma)\phi_k(\gamma)+\omega_\gamma\delta_4(\mu,\gamma)\phi_\ell(\gamma)\chi_k(\gamma)\Big)\,d\gamma\Bigg]\,d\mu\\
&= -\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\Bigg[\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)\phi_1(\mu)\phi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\mu\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)\phi_1(\mu)\chi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\gamma\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)\phi_1(\mu)\phi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\mu\omega_\gamma\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)\phi_1(\mu)\chi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\,d\mu\,d\gamma\Big)\Bigg]\\
&\quad-\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Bigg[\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)\phi_i(\mu)\phi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\mu\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)\phi_i(\mu)\chi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\gamma\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)\phi_i(\mu)\phi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\mu\omega_\gamma\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)\phi_i(\mu)\chi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\,d\mu\,d\gamma\Big)\Bigg]. \qquad (43)
\end{aligned}
$$

Before substituting P_4^a into Term 3 in (39), we integrate that term by parts to obtain

$$
\begin{aligned}
&-\rho_4\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\mu}P_4(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\,d\gamma\,d\mu\\
&\quad=-\rho_4\int_0^{\gamma_f}\left[\int_0^{\mu_f}\frac{\partial}{\partial\mu}P_4(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\,d\mu\right]\cdot\tilde{\phi}_k(\gamma)\,d\gamma\\
&\quad=-\rho_4\int_0^{\gamma_f}\left[P_4(t,\mu,\gamma)\tilde{\phi}_j(\mu)\Big|_{\mu=0}^{\mu=\mu_f}-\int_0^{\mu_f}P_4(t,\mu,\gamma)\tilde{\phi}_j'(\mu)\,d\mu\right]\cdot\tilde{\phi}_k(\gamma)\,d\gamma\\
&\quad=-\rho_4\int_0^{\gamma_f}\left[P_4(t,\mu_f,\gamma)\tilde{\phi}_j(\mu=\mu_f)-P_4(t,0,\gamma)\tilde{\phi}_j(\mu=0)-\int_0^{\mu_f}P_4(t,\mu,\gamma)\tilde{\phi}_j'(\mu)\,d\mu\right]\cdot\tilde{\phi}_k(\gamma)\,d\gamma\\
&\quad=-\rho_4\int_0^{\gamma_f}\left[P_4(t,\mu_f,\gamma)\phi_j(\mu=\mu_f)-P_4(t,0,\gamma)\phi_j(\mu=0)-\int_0^{\mu_f}P_4(t,\mu,\gamma)\tilde{\phi}_j'(\mu)\,d\mu\right]\cdot\tilde{\phi}_k(\gamma)\,d\gamma,
\end{aligned}
$$

where we have used the fact that $\tilde{\phi}_j(x)=\phi_j(x)$ when x is a nodal point. Substituting the approximate

solution, we then obtain

$$
\begin{aligned}
&-\rho_4 \int_0^{\gamma_f} \left[P_4^a(t,\mu_f,\gamma)\phi_j(\mu=\mu_f) - P_4^a(t,0,\gamma)\phi_j(\mu=0) - \int_0^{\mu_f} P_4^a(t,\mu,\gamma)\tilde{\phi}_j'(\mu)\ d\mu \right] \cdot \tilde{\phi}_k(\gamma)\ d\gamma \\
&\quad = -\rho_4 \int_0^{\gamma_f} \Bigg[\Big(\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu=\mu_f)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu=\mu_f)\cdot\phi_\ell(\gamma)\Big)\phi_j(\mu=\mu_f) \\
&\qquad\qquad - \Big(\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu=0)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu=0)\cdot\phi_\ell(\gamma)\Big)\phi_j(\mu=0) \\
&\qquad\qquad - \int_0^{\mu_f} \Big(\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma)\Big)\tilde{\phi}_j'(\mu)\ d\mu \Bigg] \cdot \tilde{\phi}_k(\gamma)\ d\gamma \\
&\quad = -\rho_4 \int_0^{\gamma_f} \Bigg[\Big(\sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_\ell(\gamma)\Big)\phi_j(\mu=\mu_f) - \Big(\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\phi_\ell(\gamma)\Big)\phi_j(\mu=0) \\
&\qquad\qquad - \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\Big[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big]\cdot\phi_\ell(\gamma) \\
&\qquad\qquad - \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\Big[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big]\cdot\phi_\ell(\gamma) \Bigg] \cdot \tilde{\phi}_k(\gamma)\ d\gamma \\
&\quad = -\rho_4 \sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_j(\mu=\mu_f)\cdot\Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_4 \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\phi_j(\mu=0)\cdot\Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_4 \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big]\cdot\Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_4 \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big]\cdot\Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big]
\end{aligned}
$$

$$
\begin{aligned}
&= -\rho_4 \sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_j(\mu=\mu_f)\cdot\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right]\\
&\quad+\rho_4\sum_{\ell=1}^{N_\gamma}P_4^{bdy,\mu}(t,\gamma_\ell)\phi_j(\mu=0)\cdot\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right]\\
&\quad+\rho_4\sum_{\ell=1}^{N_\gamma}P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\left[\int_0^{\mu_f}\phi_1(\mu)\phi_j'(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j'(\mu)\;d\mu\right]\\
&\qquad\cdot\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right]\\
&\quad+\rho_4\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\cdot\left[\int_0^{\mu_f}\phi_i(\mu)\phi_j'(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j'(\mu)\;d\mu\right]\\
&\qquad\cdot\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right].
\end{aligned}
\tag{44}
$$

Before substituting P_4^a into Term 4 in (39), we integrate that term by parts to obtain

$$
\begin{aligned}
&-\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\gamma}\Big(h_4(Fe_{pl},\gamma)P_4(t,\mu,\gamma)\Big)\cdot\tilde\phi_j(\mu)\cdot\tilde\phi_k(\gamma)\;d\gamma\;d\mu\\
&\quad=\int_0^{\mu_f}\left[-\int_0^{\gamma_f}\frac{\partial}{\partial\gamma}\Big(h_4(Fe_{pl},\gamma)P_4(t,\mu,\gamma)\Big)\cdot\tilde\phi_k(\gamma)\;d\gamma\right]\cdot\tilde\phi_j(\mu)\;d\mu\\
&\quad=\int_0^{\mu_f}\left[-h_4(Fe_{pl},\gamma)P_4(t,\mu,\gamma)\tilde\phi_k(\gamma)\Big|_{\gamma=0}^{\gamma=\gamma_f}+\int_0^{\gamma_f}h_4(Fe_{pl},\gamma)P_4(t,\mu,\gamma)\tilde\phi_k'(\gamma)\;d\gamma\right]\cdot\tilde\phi_j(\mu)\;d\mu\\
&\quad=\int_0^{\mu_f}\Bigg[-h_4(Fe_{pl},\gamma_f)P_4(t,\mu,\gamma_f)\tilde\phi_k(\gamma=\gamma_f)+h_4(Fe_{pl},0)P_4(t,\mu,0)\tilde\phi_k(\gamma=0)\\
&\qquad\qquad+\int_0^{\gamma_f}h_4(Fe_{pl},\gamma)P_4(t,\mu,\gamma)\tilde\phi_k'(\gamma)\;d\gamma\Bigg]\cdot\tilde\phi_j(\mu)\;d\mu\\
&\quad=\int_0^{\mu_f}\left[-h_4(Fe_{pl},\gamma_f)P_4(t,\mu,\gamma_f)\phi_k(\gamma=\gamma_f)+\int_0^{\gamma_f}h_4(Fe_{pl},\gamma)P_4(t,\mu,\gamma)\tilde\phi_k'(\gamma)\;d\gamma\right]\cdot\tilde\phi_j(\mu)\;d\mu,
\end{aligned}
$$

where we have applied boundary condition (37) and used the fact that $\tilde\phi_k(x)=\phi_k(x)$ when x is a nodal point. Substituting the approximate solution, we then obtain

$$
\begin{aligned}
&\int_0^{\mu_f}\left[-h_4(Fe_{pl},\gamma_f)P_4^a(t,\mu,\gamma_f)\phi_k(\gamma=\gamma_f)+\int_0^{\gamma_f}h_4(Fe_{pl},\gamma)P_4^a(t,\mu,\gamma)\tilde\phi_k'(\gamma)\;d\gamma\right]\cdot\tilde\phi_j(\mu)\;d\mu\\
&\quad=\int_0^{\mu_f}\Bigg[-h_4(Fe_{pl},\gamma_f)\Big(\sum_{\ell=1}^{N_\gamma}P_4^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\phi_\ell(\gamma=\gamma_f)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\phi_i(\mu)\phi_\ell(\gamma=\gamma_f)\Big)\phi_k(\gamma=\gamma_f)\\
&\qquad+\int_0^{\gamma_f}h_4(Fe_{pl},\gamma)\Big(\sum_{\ell=1}^{N_\gamma}P_4^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\phi_\ell(\gamma)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\phi_i(\mu)\phi_\ell(\gamma)\Big)\tilde\phi_k'(\gamma)\;d\gamma\Bigg]\cdot\tilde\phi_j(\mu)\;d\mu
\end{aligned}
$$

$$
\begin{aligned}
&= \int_0^{\mu_f} \Bigg[- h_4(Fe_{pl},\gamma_f) P_4^{bdy,\mu}(t,\gamma_f)\phi_1(\mu)\phi_k(\gamma=\gamma_f) - h_4(Fe_{pl},\gamma_f)\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_i(\mu)\phi_k(\gamma=\gamma_f) \\
&\qquad + \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\cdot\Big[\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma\Big] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\phi_i(\mu)\cdot\Big[\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma\Big]\Bigg]\cdot\tilde{\phi}_j(\mu)\ d\mu \\
&= -h_4(Fe_{pl},\gamma_f)P_4^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu\Big] \\
&\qquad - h_4(Fe_{pl},\gamma_f)\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu\Big] \\
&\qquad + \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu\Big]\cdot\Big[\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma\Big] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu\Big]\cdot\Big[\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma\Big] \\
&= -h_4(Fe_{pl},\gamma_f)P_4^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\ d\mu\Big] \\
&\qquad - h_4(Fe_{pl},\gamma_f)\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\ d\mu + \omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\ d\mu\Big] \\
&\qquad + \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\ d\mu\Big] \\
&\qquad\qquad \cdot\Big[\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma\Big] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\ d\mu + \omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\ d\mu\Big] \\
&\qquad\qquad \cdot\Big[\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma\Big]. \qquad (45)
\end{aligned}
$$

6.2.6 States Vectors and Linear ODEs

States vectors of the same form seen in (32) will be used to discretize the problem so that a linear system of ODEs of the form seen in (33) can be constructed for the class P_4 PDE.

6.2.7 Mass Matrix

The matrix M, which is called the mass matrix, will be constructed as

$$M = [M_1 + \omega_\mu M_2] \cdot * [M_3 + \omega_\gamma M_4],$$

where "$\cdot*$" denotes element-wise multiplication and the matrices M_1 through M_4 are defined based on the the four integrals in the last term of (42). Since these four integrals are identical to the four integrals in the last term of (27), M_1 through M_4 should be identical to the mass matrix components

described for class P_3, *except* that the values of N_μ, N_γ, h_μ, h_γ, ω_μ, and ω_γ corresponding to class P_4 should be used when constructing these matrices.

6.2.8 Stiffness Matrix

The matrix K, which is called the stiffness matrix, will be constructed as

$$K = K^{\mathrm{V}} + K^{\mathrm{VI}} + K^{\mathrm{VII}},$$

where components V though VII are determined by contributions from equations (43) through (45), respectively. Note that K and the other entities described here are distinct from quantities used in describing the numerical solution to the class P_3 PDE, except where otherwise noted.

The first component of the stiffness matrix is

$$K^{\mathrm{V}} = -\left(K_1^{\mathrm{V}} + \omega_\mu K_2^{\mathrm{V}} + \omega_\gamma K_3^{\mathrm{V}} + \omega_\mu\omega_\gamma K_4^{\mathrm{V}}\right),$$

where the matrices K_1^{V} through K_4^{V} are defined based on the four integrals in the last term of (43).

The matrix K_1^{V} consists of $(N_\mu - 1) \times (N_\mu - 1)$ blocks which we denote $B_{ji}^{(\mathrm{V1})}$ (where each $B_{ji}^{(\mathrm{V1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$), so

$$K_1^{\mathrm{V}} = \begin{bmatrix} B_{1,1}^{(\mathrm{V1})} & B_{1,2}^{(\mathrm{V1})} & \cdots & B_{1,N_{\mu-1}}^{(\mathrm{V1})} \\ B_{2,1}^{(\mathrm{V1})} & B_{2,2}^{(\mathrm{V1})} & \cdots & B_{2,N_{\mu-1}}^{(\mathrm{V1})} \\ \vdots & \vdots & \ddots & \vdots \\ B_{N_{\mu-1},1}^{(\mathrm{V1})} & B_{N_{\mu-1},2}^{(\mathrm{V1})} & \cdots & B_{N_{\mu-1},N_{\mu-1}}^{(\mathrm{V1})} \end{bmatrix}.$$

In this case, each block is different. The element of block $B_{j-1,i-1}^{(\mathrm{V1})}$ at position (k,ℓ) is given by

$$\left[B_{j-1,i-1}^{(\mathrm{V1})}\right]_{k\ell} = \int_0^{\mu_f}\int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_i(\mu)\phi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\; d\mu\; d\gamma,$$

where $i, j \in \{2, \ldots, N_\mu\}$ and $k, \ell \in \{1, \ldots, N_\gamma\}$.

The matrix K_2^{V} has the same structure and size as K_1^{V}, but the element of block $B_{j-1,i-1}^{(\mathrm{V2})}$ at position (k,ℓ) is now given by

$$\left[B_{j-1,i-1}^{(\mathrm{V2})}\right]_{k\ell} = \int_0^{\mu_f}\int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_i(\mu)\chi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\; d\mu\; d\gamma.$$

The matrix K_3^{V} also has the same structure and size as K_1^{V}, but the element of block $B_{j-1,i-1}^{(\mathrm{V3})}$ at position (k,ℓ) is given by

$$\left[B_{j-1,i-1}^{(\mathrm{V3})}\right]_{k\ell} = \int_0^{\mu_f}\int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_i(\mu)\phi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\; d\mu\; d\gamma.$$

Finally, the matrix K_4^{V} has the same structure and size as K_1^{V}, but the element of block $B_{j-1,i-1}^{(\mathrm{V4})}$ at position (k,ℓ) is given by

$$\left[B_{j-1,i-1}^{(\mathrm{V4})}\right]_{k\ell} = \int_0^{\mu_f}\int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_i(\mu)\chi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\; d\mu\; d\gamma.$$

The second component of the stiffness matrix is

$$K^{\mathrm{VI}} = \rho_4 \left[K_1^{\mathrm{VI}} + \omega_\mu K_2^{\mathrm{VI}}\right] \cdot * \left[K_3^{\mathrm{VI}} + \omega_\gamma K_4^{\mathrm{VI}}\right] - \rho_4 K_5^{\mathrm{VI}},$$

where "$\cdot *$" denotes element-wise multiplication, the matrices K_1^{VI} through K_4^{VI} are defined based on the four integrals in the last term of (44), and K_5^{VI} is defined based on the integrals in the first term of (44).

Since the four integrals in the last term of (44) are identical to the four integrals in the last term of (30), K_1^{VI} through K_4^{VI} should be identical to the matrices K_1^{III} through K_4^{III} described for class P_3, *except* that the values of N_μ, N_γ, h_μ, h_γ, ω_μ, and ω_γ corresponding to class P_4 should be used when constructing these matrices.

Since the integrals in the first term of (44) are identical to those in the first term of (30), K_5^{VI} should be identical to the matrix K_5^{III} described for class P_3, *except* that the values of N_μ, N_γ, h_μ, h_γ, ω_μ, and ω_γ corresponding to class P_4 should be used when constructing this matrix.

The third component of the stiffness matrix is

$$K^{\mathrm{VII}} = \left[K_1^{\mathrm{VII}} + \omega_\mu K_2^{\mathrm{VII}}\right] \cdot * \left[K_3^{\mathrm{VII}} + \omega_\gamma K_4^{\mathrm{VII}}\right] - h_4(Fe_{pl}, \gamma_f) K_5^{\mathrm{VII}},$$

where "$\cdot *$" denotes element-wise multiplication, the matrices K_1^{VII} through K_4^{VII} are defined based on the four integrals in the last term of (45), and K_5^{VII} is defined based on the integrals in the second term of (45).

Since the first integral in the last term of (45) is identical to the first integral in the last term of (42), K_1^{VII} should be identical to the mass matrix component M_1 for class P_4. Also, since the second integral in the last term of (45) is identical to the second integral in the last term of (42), K_2^{VII} should be identical to the mass matrix component M_2 for class P_4.

The matrix K_3^{VII} is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(\mathrm{VII3})}$. We define

$$K_3^{\mathrm{VII}} = \begin{bmatrix} B^{(\mathrm{VII3})} & B^{(\mathrm{VII3})} & \dots & B^{(\mathrm{VII3})} \\ B^{(\mathrm{VII3})} & B^{(\mathrm{VII3})} & \dots & B^{(\mathrm{VII3})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{VII3})} & B^{(\mathrm{VII3})} & \dots & B^{(\mathrm{VII3})} \end{bmatrix},$$

where $B^{(\mathrm{VII3})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(\mathrm{VII3})}]_{k\ell} = \int_0^{\gamma_f} h_4(Fe_{pl}, \gamma) \phi_\ell(\gamma) \phi_k'(\gamma) \, d\gamma.$$

The variable Fe_{pl} is time-dependent, so this subcomponent of K^{VII} will have to be recomputed at each time step. If we let

$$f(\gamma) = h_4(Fe_{\mathrm{curr}}, \gamma), \tag{46}$$

where Fe_{curr} is the current value of Fe_{pl}, and then evaluate this function at the nodes we used to partition $[0, \gamma_f]$, we can approximate f using a piecewise linear interpolation. If we let $f_i = f(\gamma_i)$, then we can approximate the integral defining $[B^{(\mathrm{VII3})}]_{k\ell}$ as

$$\int_0^{\gamma_f} f(\gamma) \phi_\ell(\gamma) \phi_k'(\gamma) \, d\gamma = \begin{cases} -\frac{1}{3} f_1 - \frac{1}{6} f_2 & \text{if } k = \ell = 1 \\ \frac{1}{6} f_{N_\gamma - 1} + \frac{1}{3} f_{N_\gamma} & \text{if } k = \ell = N_\gamma \\ \frac{1}{6} f_{k-1} - \frac{1}{6} f_{k+1} & \text{if } k = \ell \notin \{1, N_\gamma\} \\ \frac{1}{3} f_{k-1} + \frac{1}{6} f_k & \text{if } k - \ell = 1 \\ -\frac{1}{6} f_k - \frac{1}{3} f_{k+1} & \text{if } \ell - k = 1 \\ 0 & \text{otherwise.} \end{cases}$$

Thus, the identical blocks that make up K_3^{VII} can be written

$$B^{(\text{VII3})} = \frac{1}{6}\begin{bmatrix} (-2f_1 - f_2) & (-f_1 - 2f_2) & 0 & \cdots & 0 \\ (2f_1 + f_2) & (f_1 - f_3) & (-f_2 - 2f_3) & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & \left(2f_{N_\gamma-2} + f_{N_\gamma-1}\right) & \left(f_{N_\gamma-2} - f_{N_\gamma}\right) & \left(-f_{N_\gamma-1} - 2f_{N_\gamma}\right) \\ 0 & \cdots & 0 & \left(2f_{N_\gamma-1} + f_{N_\gamma}\right) & \left(f_{N_\gamma-1} + 2f_{N_\gamma}\right) \end{bmatrix}.$$

The matrix K_4^{VII} has the same form as K_3^{VII} except that the block matrix $B^{(\text{VII4})}$ has entries given by

$$[B^{(\text{VII4})}]_{k\ell} = \int_0^{\gamma_f} h_4(Fe_{pl}, \gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\, d\gamma.$$

If we once again let f be the function defined in (46) and let $f_i = f(\gamma_i)$, then we can approximate the integral defining $[B^{(\text{VII4})}]_{k\ell}$ as

$$\int_0^{\gamma_f} f(\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\, d\gamma = \begin{cases} -\frac{1}{6}f_k & \text{if } k = \ell = 1 \in \{1, N_\gamma\} \\ -\frac{1}{3}f_k & \text{if } k = \ell \notin \{1, N_\gamma\} \\ \frac{1}{6}f_{k-1} & \text{if } k - \ell = 1 \\ \frac{1}{6}f_{k+1} & \text{if } \ell - k = 1 \\ 0 & \text{otherwise.} \end{cases}$$

Thus, the identical blocks that make up K_4^{VII} can be written

$$B^{(\text{VII4})} = \frac{1}{6}\begin{bmatrix} -f_1 & f_2 & 0 & \cdots & 0 \\ f_1 & -2f_2 & f_3 & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & f_{N_\gamma-2} & -2f_{N_\gamma-1} & f_{N_\gamma} \\ 0 & \cdots & 0 & f_{N_\gamma-1} & -f_{N_\gamma} \end{bmatrix}.$$

The matrix K_5^{VII} consists of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks which we denote $B^{(\text{VII5})}$, so

$$K_5^{\text{VII}} = \begin{bmatrix} B^{(\text{VII5})} & B^{(\text{VII5})} & \cdots & B^{(\text{VII5})} \\ B^{(\text{VII5})} & B^{(\text{VII5})} & \cdots & B^{(\text{VII5})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\text{VII5})} & B^{(\text{VII5})} & \cdots & B^{(\text{VII5})} \end{bmatrix}.$$

Note that the term responsible for generating this matrix is

$$\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\;d\mu\Big].$$

Because the only $A_{i,\ell}(t)$ terms that are present are those for which $\ell = N_\gamma$, and because $\phi_k(\gamma = \gamma_f)$ is only nonzero when $k = N_\gamma$, the only nonzero elements in this matrix are those corresponding to $k = \ell = N_\gamma$ (the lower right-hand element of each block.) Thus, if we define $D \in \mathbb{R}^{N_\gamma \times N_\gamma}$ as

$$D=\begin{bmatrix}0&0&\cdots&0\\0&\ddots&\ddots&\vdots\\\vdots&\ddots&0&0\\0&\cdots&0&1\end{bmatrix},$$

then

$$K_5^{\mathrm{VII}}=\begin{bmatrix}D&D&\cdots&D\\D&D&\cdots&D\\\vdots&\vdots&\ddots&\vdots\\D&D&\cdots&D\end{bmatrix}\cdot*\left[M_1+\omega_\mu M_2\right],$$

where "$\cdot*$" denotes element-wise multiplication.

6.2.9 The Boundary Conditions Vector

The only item in (33) (for the class P_4 ODEs) which we have yet to describe is the vector b, which incorporates all contributions from the boundary conditions stated in (38). This vector will be constructed as

$$b = b^{\mathrm{VI}} + b^{\mathrm{VII}} + b^{\mathrm{VIII}} + b^{\mathrm{IX}},$$

where components VI though IX are determined by contributions from equations (42) through (45), respectively.

The vector $b^{\mathrm{VI}} \in \mathbb{R}^{(N_\mu-1)N_\gamma}$ is generated by the term

$$-\sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_4^{bdy,\mu}(t,\gamma_\ell)\cdot\left[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\;d\mu\right]\cdot\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right]$$

in (42), where we have changed the sign to place the vector on the right-hand side of (33). This vector has the same block form as the states vectors described in (32), so $j \in \{2,\ldots,N_\mu\}$ indicates a specific block and $k \in \{1,\ldots,N\gamma\}$ indicates the position within that block. The expression in the first pair of brackets above is only nonzero for $j = 2$, so only entries in the first block of b^{VI} are nonzero. Now if we consider the vector $\dot{v} \in \mathbb{R}^{N_\gamma}$ given by $\dot{v}_\ell = \frac{\partial}{\partial t}P_4^{bdy,\mu}(t,\gamma_\ell)$ and define a matrix $C^{(\mathrm{VI})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\mathrm{VI})}]_{k\ell}=\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right],$$

then

$$b^{\mathrm{VI}} = -\left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12}\right) \cdot \begin{bmatrix} C^{(\mathrm{VI})}\dot{v} \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N^\gamma}$. Revisiting the derivation for the mass matrix components M_3 and M_4, it is clear that

$$C^{(\mathrm{VI})} = B^{(3)} + \omega_\gamma B^{(4)}.$$

Observe that the expressions for $C^{(\mathrm{VI})}$ and $C^{(\mathrm{I})}$ as well as the expressions for $b^{(\mathrm{VI})}$ and $b^{(\mathrm{I})}$ are identical. However, the actual data structures may differ since here we must use values of N_μ, h_μ, and ω_μ corresponding to class P_4.

The vector $b^{\mathrm{VII}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ is generated by the term

$$\begin{aligned} -\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t, \gamma_\ell) \cdot \Bigg[& \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\phi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\, d\mu\, d\gamma \Big) \\ & + \omega_\mu \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\chi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\, d\mu\, d\gamma \Big) \\ & + \omega_\gamma \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\phi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\, d\mu\, d\gamma \Big) \\ & + \omega_\mu\omega_\gamma \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\chi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\, d\mu\, d\gamma \Big) \Bigg] \end{aligned}$$

in (43). This vector has the same block form as the states vectors described in (32), so $j \in \{2, \ldots, N_\mu\}$ indicates a specific block and $k \in \{1, \ldots, N\gamma\}$ indicates the position within that block. Since the expressions $\phi_1(\mu)\phi_j(\mu)$ and $\phi_1(\mu)\chi_j(\mu)$ are only nonzero for $j = 2$, only entries in the first block of b^{VII} are nonzero. Now, if we consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_4^{bdy,\mu}(t, \gamma_\ell)$ and define a matrix $C^{(\mathrm{VII})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$\begin{aligned} [C^{(\mathrm{VII})}]_{k\ell} = -\Bigg[& \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\phi_2(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\, d\mu\, d\gamma \Big) \\ & + \omega_\mu \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\chi_2(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\, d\mu\, d\gamma \Big) \\ & + \omega_\gamma \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\phi_2(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\, d\mu\, d\gamma \Big) \\ & + \omega_\mu\omega_\gamma \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_4(\mu,\gamma)\phi_1(\mu)\chi_2(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\, d\mu\, d\gamma \Big) \Bigg], \end{aligned}$$

then

$$b^{\text{VII}} = \begin{bmatrix} C^{(\text{VII})}v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N^\gamma}$.

The vector $b^{\text{VIII}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ can be computed as

$$b^{\text{VIII}} = b_1^{\text{VIII}} + b_2^{\text{VIII}},$$

where b_1^{VIII} is generated by the term

$$\rho_4 \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t, \gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\phi_j'(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j'(\mu)\ d\mu \right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right]$$

in (44) and b_2^{VIII} is generated by the term

$$\rho_4 \sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t, \gamma_\ell)\phi_j(\mu = 0) \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right],$$

also in (44). These vectors have the same block form as the states vectors described in (32), so $j \in \{2, \ldots, N_\mu\}$ indicates a specific block and $k \in \{1, \ldots, N\gamma\}$ indicates the position within that block.

Note that $\phi_1(\mu)\phi_j'(\mu)$ and $\phi_1(\mu)\chi_j'(\mu)$ are only nonzero for $j = 2$, so only entries in the first block of b_1^{VIII} are nonzero. If we consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_4^{bdy,\mu}(t, \gamma_\ell)$ and define a matrix $C^{(\text{VIII1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\text{VIII1})}]_{k\ell} = \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right],$$

then

$$b_1^{\text{VIII}} = \rho_4 \left(\frac{1}{2} + \frac{\omega_\mu}{6} \right) \cdot \begin{bmatrix} C^{(\text{VIII1})}v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N^\gamma}$. Note that $C^{(\text{VIII1})} = C^{(\text{VI})}$. Also, note that $\phi_j(\mu = 0) = 0$ for all $j \in \{2, \ldots, N_\mu\}$, so $b_2^{\text{VIII}} = (0, \ldots, 0)^T$. Therefore, $b^{\text{VIII}} = b_1^{\text{VIII}}$.

The vector $b^{\mathrm{IX}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ can be computed as

$$b^{\mathrm{IX}} = b_1^{\mathrm{IX}} + b_2^{\mathrm{IX}},$$

where b_1^{IX} is generated by the term

$$\sum_{\ell=1}^{N_\gamma} P_4^{bdy,\mu}(t,\gamma_\ell) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu \Big] \cdot \Big[\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma \Big]$$

in (45) and b_2^{IX} is generated by the term

$$-h_4(Fe_{pl},\gamma_f)P_4^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu \Big],$$

also in (45). These vectors have the same block form as the states vectors described in (32), so $j \in \{2,\dots,N_\mu\}$ indicates a specific block and $k \in \{1,\dots,N\gamma\}$ indicates the position within that block.

Note that $\phi_1(\mu)\phi_j(\mu)$ and $\phi_1(\mu)\chi_j(\mu)$ are only nonzero for $j = 2$ and, so only entries in the first block of b_1^{IX} are nonzero. If we once again consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_4^{bdy,\mu}(t,\gamma_\ell)$ and define a matrix $C^{(\mathrm{IX1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\mathrm{IX1})}]_{k\ell} = \left[\int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} h_4(Fe_{pl},\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma \right],$$

then

$$b_1^{\mathrm{IX}} = \left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12} \right) \cdot \begin{bmatrix} C^{(\mathrm{IX1})} v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0,\dots,0)^T \in \mathbb{R}^{N^\gamma}$. Because the variable Fe_{pl} is time-dependent, the matrix $C^{(\mathrm{IX1})}$ will have to be recomputed at each time step. If we let f be the function defined in (46) and let $f_i = f(\gamma_i)$, then we can approximate the integral defining $[C^{(\mathrm{IX1})}]_{k\ell}$ as was done for $[B^{(\mathrm{VII3})}]_{k\ell}$ and $[B^{(\mathrm{VII4})}]_{k\ell}$. In fact,

$$C^{(\mathrm{IX1})} = B^{(\mathrm{VII3})} + \omega_\gamma B^{(\mathrm{VII4})}.$$

For the vector b_2^{IX}, note again that the integrals in the brackets are only nonzero for $j = 2$. Also, because $\phi_k(\gamma = \gamma_f)$ is only nonzero when $k = N_\gamma$, the only nonzero element in this vector is the last

element of the first block. In fact,

$$b_2^{\mathrm{IX}} = -h_4(Fe_{pl},\gamma_f)P_4^{bdy,\mu}(t,\gamma_f)\left(\frac{h_\mu}{6}+\omega_\mu\frac{h_\mu}{12}\right)\cdot\left[\begin{array}{c}0\\ \vdots\\ 0\\ 1\\ \hline 0\\ \vdots\\ 0\\ \hline \vdots\\ \hline 0\\ \vdots\\ 0\end{array}\right].$$

6.2.10 Testing Numerical Solver for Class $\mathbf{P}_4$ PDE

To test the numerical solution technique described above, we once again apply the method of synthetic solutions. To begin, we append a forcing term to the PDE given in (36) to obtain the new PDE

$$\begin{aligned}\frac{\partial}{\partial t}\tilde{P}_4(t,\mu,\gamma) = &-\delta_4(\mu,\gamma)\tilde{P}_4(t,\mu,\gamma) - \rho_4\frac{\partial}{\partial\mu}\tilde{P}_4(t,\mu,\gamma)\\ &-\frac{\partial}{\partial\gamma}\left[h_4(Fe_{pl},\gamma)\tilde{P}_4(t,\mu,\gamma)\right] + f(t,\mu,\gamma).\end{aligned} \tag{47}$$

Next, we select our "known solution" to be

$$\tilde{P}_4(t,\mu,\gamma) = \left(\sin\frac{2\pi t}{3}+2\right)\cdot\left(\frac{\mu}{\mu_f}+1\right)\cdot\left(e^{\gamma/\gamma_f}-1\right).$$

This solution was chosen to have a temporal period of 3 days since the solver can generate solutions for that period in a reasonable amount of time. Solving (47) for $f(t,\mu,\gamma)$ and then substituting in the known solution, we obtain

$$\begin{aligned}f(t,\mu,\gamma) = &\frac{\partial}{\partial t}\tilde{P}_4(t,\mu,\gamma) + \delta_4(\mu,\gamma)\tilde{P}_4(t,\mu,\gamma) + \rho_4\frac{\partial}{\partial\mu}\tilde{P}_4(t,\mu,\gamma)\\ &+\frac{\partial}{\partial\gamma}\left[h_4(Fe_{pl},\gamma)\tilde{P}_4(t,\mu,\gamma)\right]\end{aligned}$$

$$
\begin{aligned}
f(t,\mu,\gamma) = &\left(\frac{2\pi}{3}\cos\frac{2\pi t}{3}\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right) \\
&+ \delta_4(\mu,\gamma)\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right) \\
&+ \rho_4\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{1}{\mu_f}\right)\left(e^{\gamma/\gamma_f}-1\right) \\
&+ \left[\frac{\partial}{\partial\gamma}h_4(Fe_{pl},\gamma)\right]\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right) \\
&+ h_4(Fe_{pl},\gamma)\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(\frac{1}{\gamma_f}e^{\gamma/\gamma_f}\right).
\end{aligned}
$$

Now, the weak form for the class P_4 PDE becomes

$$
\begin{aligned}
&\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial t}P_4(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 1]} \\
&\quad = -\int_0^{\mu_f}\int_0^{\gamma_f}\delta_4(\mu,\gamma)P_4(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 2]} \\
&\qquad -\rho_4\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\mu}P_4(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 3]} \\
&\qquad -\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\gamma}\Big(h_4(Fe_{pl},\gamma)P_4(t,\mu,\gamma)\Big)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 4]} \\
&\qquad +\int_0^{\mu_f}\int_0^{\gamma_f}f(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Forcing Term]}.
\end{aligned}
$$

Thus, the ODE for the row corresponding to each (j,k) in (33) will have an additional "forcing term". These additional terms force the numerical solver to return the desired solution $\tilde{P}_4(t,\mu,\gamma)$. Note that the initial conditions must be set to

$$
\tilde{P}_4(0,\mu,\gamma) = P_4^{init}(\mu,\gamma) = 2\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right)
$$

and the $\mu = 0$ boundary conditions must be set to

$$
\tilde{P}_4(t,0,\gamma) = \tilde{P}_4^{bdy,\mu}(t,\gamma) = \left(\sin\frac{2\pi t}{3}+2\right)\cdot\left(e^{\gamma/\gamma_f}-1\right)
$$

when using this validation technique.

6.3 Numerical Solution of Class P_5 PDE

6.3.1 Description of Initial-Value/Boundary-Value problem

The PDE (12) describing cells in class P_5 can be restated as

$$
\begin{aligned}
\frac{\partial}{\partial t}P_5(t,\mu,\gamma) = &-\delta_5\left(\mu,\gamma,EPO,\frac{d}{dt}EPO\right)P_5(t,\mu,\gamma) - \rho_5\frac{\partial}{\partial\mu}P_5(t,\mu,\gamma) \\
&- \frac{\partial}{\partial\gamma}\left[h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\right]. \qquad (48)
\end{aligned}
$$

Here, we have replaced μ_5 by μ to simplify notation in the sections that follow. This variable μ and the variables N_μ, μ_f, h_μ, and ω_μ described in the following sections are distinct from those used for classes P_3 and P_4.

Using the same notational conventions, the initial condition is given by

$$P_5(0,\mu,\gamma) = P_5^{init}(\mu,\gamma)$$

for $(\mu,\gamma) \in (0,\mu_f) \times [0,\gamma_f]$.

The $\gamma = 0$ boundary condition is given by

$$h_5(Fe_{pl},0)P_5(t,\mu,0) = 0 \tag{49}$$

for $\mu \in [0,\mu_f]$ and the $\mu = 0$ boundary condition is given by

$$P_5(t,0,\gamma) = P_5^{bdy,\mu}(t,\gamma) = P_4(t,(\mu_4)_f,\gamma) \tag{50}$$

for $\gamma \in [0,\gamma_f]$.

6.3.2 Mesh on "Spatial" Domain

We partition $[0,\mu_f]$ with N_μ equally-spaced nodes $\{0 = \mu_1, \mu_2, \ldots, \mu_{N_\mu} = \mu_f\}$ using a step size

$$h_\mu = \frac{\mu_f}{(N_\mu - 1)}.$$

Similarly, we partition $[0,\gamma_f]$ with N_γ equally-spaced nodes $\{0 = \gamma_1, \gamma_2, \ldots, \gamma_{N_\gamma} = \gamma_f\}$ using a step size

$$h_\gamma = \frac{\gamma_f}{(N_\gamma - 1)}.$$

We ensure that N_γ is odd so that a node exists at $\frac{\gamma_f}{2}$.

By pairing nodes from these two partitions, we can construct a mesh on $[0,\mu_f] \times [0,\gamma_f]$ consisting of the grid points $\big\{(\mu_i,\gamma_\ell) \mid i \in \{1,2,\ldots,N_\mu\} \text{ and } \ell \in \{1,2,\ldots,N_\gamma\}\big\}$.

6.3.3 Test Functions

In order to develop the weak formulation of (48), we use test functions of the same form as those that were used for classes P_3 and P_4.

6.3.4 Weak Formulation

We multiply (48) by test functions $\tilde{\phi}_j(\mu)$ and $\tilde{\phi}_k(\gamma)$ and integrate over the entire spatial domain $[0,\mu_f] \times [0,\gamma_f]$ to obtain the weak formulation

$$\begin{aligned}
&\int_0^{\mu_f}\int_0^{\gamma_f} \frac{\partial}{\partial t}P_5(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\; d\gamma\; d\mu \quad \text{[Term 1]} \\
&\qquad = -\int_0^{\mu_f}\int_0^{\gamma_f} \delta_5\left(\mu,\gamma,EPO,\frac{d}{dt}EPO\right)P_5(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\; d\gamma\; d\mu \quad \text{[Term 2]} \\
&\qquad\quad - \rho_5\int_0^{\mu_f}\int_0^{\gamma_f} \frac{\partial}{\partial \mu}P_5(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\; d\gamma\; d\mu \quad \text{[Term 3]} \\
&\qquad\quad - \int_0^{\mu_f}\int_0^{\gamma_f} \frac{\partial}{\partial \gamma}\Big(h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\Big)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\; d\gamma\; d\mu \quad \text{[Term 4]}.
\end{aligned} \tag{51}$$

6.3.5 Numerical Solution

Now, we assume that the approximate solution can be expressed in the form

$$\begin{aligned}
P_5^a(t,\mu,\gamma) &= \sum_{i=1}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\
&= \sum_{\ell=1}^{N_\gamma} P_5(t,\mu_1,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\
&= \sum_{\ell=1}^{N_\gamma} P_5(t,0,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma) \\
&= \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma), \qquad (52)
\end{aligned}$$

where $A_{i,\ell}(t)$ represents the approximate value of $P_5(t,\mu_i,\gamma_\ell)$. As was the case for the numerical solutions for P_3 and P_4, we can visualize the $N_\mu \times N_\gamma$ coefficient matrix $A(t)$ as an array of function values corresponding to a set of points in the region $[0,\mu_f]\times[0,\gamma_f]$. Again, since each entry corresponding to $i=1$ is a known quantity based on the boundary condition (50), this array can be expressed as

$$\begin{array}{c} \\ (i=1) \\ (i=2) \\ \vdots \\ (i=N_\mu) \end{array}
\begin{array}{c}
\begin{array}{cccc} (\ell=1) & (\ell=2) & \cdots & (\ell=N_\gamma) \end{array} \\
\left[\begin{array}{cccc}
P_5^{bdy,\mu}(t,\gamma_1) & P_5^{bdy,\mu}(t,\gamma_2) & \cdots & P_5^{bdy,\mu}(t,\gamma_f) \\
A_{2,1}(t) & A_{2,2}(t) & \cdots & A_{2,N_\gamma}(t) \\
\vdots & \vdots & & \vdots \\
A_{N_\mu,1}(t) & A_{N_\mu,2}(t) & \cdots & A_{N_\mu,N_\gamma}(t)
\end{array}\right]
\end{array}$$

Differentiating (52) with respect to time, we see that

$$\frac{\partial}{\partial t}P_5^a(t,\mu,\gamma) = \sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma), \qquad (53)$$

where $\dot{A}_{i,\ell}(t)$ represents the approximate value of $\frac{\partial}{\partial t}P_5(t,\mu_i,\gamma_\ell)$ at each grid point of the mesh (except those on the $\mu=0$ boundary). Note that $\frac{\partial}{\partial t}P_5^{bdy,\mu}(t,\gamma_\ell)$ can be computed by taking the time derivative of $P_4(t,(\mu_4)_f,\gamma)$. In practice, a numerical solution P_4^a will be used, so a numerical approximation of this time derivative can be computed.

Our problem now consists of finding $\{A_{i,\ell}(t) \mid i\in\{2,3,\ldots,N_\mu\} \text{ and } \ell\in\{1,2,\ldots,N_\gamma\}\}$. We can accomplish this by constructing and solving a system of ODEs consisting of a total of $(N_\mu-1)N_\gamma$ equations. To obtain this system of ODEs, we replace P_5 and $\frac{\partial}{\partial t}P_5$ in (51) by the approximations P_5^a and $\frac{\partial}{\partial t}P_5^a$ described in (52) and (53). For example, Term 1 in (51) becomes

$$\begin{aligned}
&\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial t}P_5^a(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \\
&\quad= \int_0^{\mu_f}\int_0^{\gamma_f}\Big(\sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}\dot{A}_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma)\Big) \\
&\qquad\qquad \cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu
\end{aligned}$$

$$
\begin{aligned}
&= \sum_{\ell=1}^{N_\gamma} \frac{\partial}{\partial t} P_5^{bdy,\mu}(t,\gamma_\ell) \cdot \int_0^{\mu_f} \int_0^{\gamma_f} \phi_1(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} \dot{A}_{i,\ell}(t) \cdot \int_0^{\mu_f} \int_0^{\gamma_f} \phi_i(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&= \sum_{\ell=1}^{N_\gamma} \frac{\partial}{\partial t} P_5^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu\right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} \dot{A}_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu\right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right] \\
&= \sum_{\ell=1}^{N_\gamma} \frac{\partial}{\partial t} P_5^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu\right] \\
&\qquad\qquad \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma\right] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} \dot{A}_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \phi_i(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_i(\mu)\chi_j(\mu)\ d\mu\right] \\
&\qquad\qquad \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma\right]. \qquad (54)
\end{aligned}
$$

Substituting P_5^a into Term 2 in (51) and abbreviating $\delta_5\left(\mu,\gamma,EPO,\frac{d}{dt}EPO\right)$ as $\delta_5(\mu,\gamma,E)$, we obtain

$$
\begin{aligned}
&- \int_0^{\mu_f} \int_0^{\gamma_f} \delta_5(\mu,\gamma,E) P_5^a(t,\mu,\gamma) \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = - \int_0^{\mu_f} \int_0^{\gamma_f} \delta_5(\mu,\gamma,E) \cdot \Big(\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell) \cdot \phi_1(\mu) \cdot \phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \phi_i(\mu) \cdot \phi_\ell(\gamma)\Big) \\
&\qquad\qquad \cdot \tilde{\phi}_j(\mu) \cdot \tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = - \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell) \int_0^{\mu_f} \int_0^{\gamma_f} \delta_5(\mu,\gamma,E)\phi_1(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\qquad - \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \int_0^{\mu_f} \int_0^{\gamma_f} \delta_5(\mu,\gamma,E)\phi_i(\mu)\phi_\ell(\gamma)\tilde{\phi}_j(\mu)\tilde{\phi}_k(\gamma)\ d\gamma\ d\mu \\
&\quad = - \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j(\mu) \cdot \left[\int_0^{\gamma_f} \delta_5(\mu,\gamma,E)\phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right]\ d\mu\right] \\
&\qquad - \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t) \cdot \left[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j(\mu) \cdot \left[\int_0^{\gamma_f} \delta_5(\mu,\gamma,E)\phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma\right]\ d\mu\right]
\end{aligned}
$$

$$
\begin{aligned}
&= -\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\int_0^{\mu_f}\Bigg[\Big(\phi_1(\mu)\phi_j(\mu)+\omega_\mu\phi_1(\mu)\chi_j(\mu)\Big)\\
&\qquad\qquad\cdot\int_0^{\gamma_f}\Big(\delta_5(\mu,\gamma,E)\phi_\ell(\gamma)\phi_k(\gamma)+\omega_\gamma\delta_5(\mu,\gamma,E)\phi_\ell(\gamma)\chi_k(\gamma)\Big)\,d\gamma\Bigg]\,d\mu\\
&\quad -\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\int_0^{\mu_f}\Bigg[\Big(\phi_i(\mu)\phi_j(\mu)+\omega_\mu\phi_i(\mu)\chi_j(\mu)\Big)\\
&\qquad\qquad\cdot\int_0^{\gamma_f}\Big(\delta_5(\mu,\gamma,E)\phi_\ell(\gamma)\phi_k(\gamma)+\omega_\gamma\delta_5(\mu,\gamma,E)\phi_\ell(\gamma)\chi_k(\gamma)\Big)\,d\gamma\Bigg]\,d\mu\\
&= -\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\Bigg[\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5(\mu,\gamma,E)\phi_1(\mu)\phi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\mu\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5(\mu,\gamma,E)\phi_1(\mu)\chi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\gamma\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5(\mu,\gamma,E)\phi_1(\mu)\phi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\mu\omega_\gamma\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5(\mu,\gamma,E)\phi_1(\mu)\chi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\,d\mu\,d\gamma\Big)\Bigg]\\
&\quad -\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Bigg[\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5(\mu,\gamma,E)\phi_i(\mu)\phi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\mu\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5(\mu,\gamma,E)\phi_i(\mu)\chi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\gamma\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5(\mu,\gamma,E)\phi_i(\mu)\phi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\,d\mu\,d\gamma\Big)\\
&\qquad\qquad+\omega_\mu\omega_\gamma\Big(\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5(\mu,\gamma,E)\phi_i(\mu)\chi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\,d\mu\,d\gamma\Big)\Bigg]. \qquad (55)
\end{aligned}
$$

Before substituting P_5^a into Term 3 in (51), we integrate that term by parts to obtain

$$
\begin{aligned}
&-\rho_5\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\mu}P_5(t,\mu,\gamma)\cdot\tilde\phi_j(\mu)\cdot\tilde\phi_k(\gamma)\,d\gamma\,d\mu\\
&\quad=-\rho_5\int_0^{\gamma_f}\Bigg[\int_0^{\mu_f}\frac{\partial}{\partial\mu}P_5(t,\mu,\gamma)\cdot\tilde\phi_j(\mu)\,d\mu\Bigg]\cdot\tilde\phi_k(\gamma)\,d\gamma\\
&\quad=-\rho_5\int_0^{\gamma_f}\Bigg[P_5(t,\mu,\gamma)\tilde\phi_j(\mu)\Big|_{\mu=0}^{\mu=\mu_f}-\int_0^{\mu_f}P_5(t,\mu,\gamma)\tilde\phi_j'(\mu)\,d\mu\Bigg]\cdot\tilde\phi_k(\gamma)\,d\gamma\\
&\quad=-\rho_5\int_0^{\gamma_f}\Bigg[P_5(t,\mu_f,\gamma)\tilde\phi_j(\mu=\mu_f)-P_5(t,0,\gamma)\tilde\phi_j(\mu=0)-\int_0^{\mu_f}P_5(t,\mu,\gamma)\tilde\phi_j'(\mu)\,d\mu\Bigg]\cdot\tilde\phi_k(\gamma)\,d\gamma\\
&\quad=-\rho_5\int_0^{\gamma_f}\Bigg[P_5(t,\mu_f,\gamma)\phi_j(\mu=\mu_f)-P_5(t,0,\gamma)\phi_j(\mu=0)-\int_0^{\mu_f}P_5(t,\mu,\gamma)\tilde\phi_j'(\mu)\,d\mu\Bigg]\cdot\tilde\phi_k(\gamma)\,d\gamma,
\end{aligned}
$$

where we have used the fact that $\tilde\phi_j(x)=\phi_j(x)$ when x is a nodal point. Substituting the approximate

solution, we then obtain

$$
\begin{aligned}
&-\rho_5 \int_0^{\gamma_f} \left[P_5^a(t,\mu_f,\gamma)\phi_j(\mu=\mu_f) - P_5^a(t,0,\gamma)\phi_j(\mu=0) - \int_0^{\mu_f} P_5^a(t,\mu,\gamma)\tilde{\phi}_j'(\mu)\ d\mu \right] \cdot \tilde{\phi}_k(\gamma)\ d\gamma \\
&\quad = -\rho_5 \int_0^{\gamma_f} \Bigg[\Big(\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu=\mu_f)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu=\mu_f)\cdot\phi_\ell(\gamma)\Big)\phi_j(\mu=\mu_f) \\
&\qquad\qquad - \Big(\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu=0)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu=0)\cdot\phi_\ell(\gamma)\Big)\phi_j(\mu=0) \\
&\qquad\qquad - \int_0^{\mu_f} \Big(\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\phi_1(\mu)\cdot\phi_\ell(\gamma) + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\phi_i(\mu)\cdot\phi_\ell(\gamma)\Big)\tilde{\phi}_j'(\mu)\ d\mu \Bigg] \cdot \tilde{\phi}_k(\gamma)\ d\gamma \\
&\quad = -\rho_5 \int_0^{\gamma_f} \Bigg[\Big(\sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_\ell(\gamma)\Big)\phi_j(\mu=\mu_f) - \Big(\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\phi_\ell(\gamma)\Big)\phi_j(\mu=0) \\
&\qquad\qquad - \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\Big[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big]\cdot\phi_\ell(\gamma) \\
&\qquad\qquad - \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\Big[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big]\cdot\phi_\ell(\gamma) \Bigg] \cdot \tilde{\phi}_k(\gamma)\ d\gamma \\
&\quad = -\rho_5 \sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_j(\mu=\mu_f)\cdot\Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_5 \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\phi_j(\mu=0)\cdot\Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_5 \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f} \phi_1(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big]\cdot\Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big] \\
&\qquad + \rho_5 \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f} \phi_i(\mu)\tilde{\phi}_j'(\mu)\ d\mu \Big]\cdot\Big[\int_0^{\gamma_f} \phi_\ell(\gamma)\tilde{\phi}_k(\gamma)\ d\gamma \Big]
\end{aligned}
$$

$$
\begin{aligned}
&= -\rho_5 \sum_{\ell=1}^{N_\gamma} A_{N_\mu,\ell}(t)\phi_j(\mu=\mu_f)\cdot\Big[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\Big]\\
&\quad+\rho_5\sum_{\ell=1}^{N_\gamma}P_5^{bdy,\mu}(t,\gamma_\ell)\phi_j(\mu=0)\cdot\Big[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\Big]\\
&\quad+\rho_5\sum_{\ell=1}^{N_\gamma}P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\phi_j'(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j'(\mu)\;d\mu\Big]\\
&\qquad\cdot\Big[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\Big]\\
&\quad+\rho_5\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j'(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j'(\mu)\;d\mu\Big]\\
&\qquad\cdot\Big[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\Big].
\end{aligned}
\tag{56}
$$

Before substituting P_5^a into Term 4 in (51), we integrate that term by parts to obtain

$$
\begin{aligned}
&-\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\gamma}\Big(h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\Big)\cdot\tilde\phi_j(\mu)\cdot\tilde\phi_k(\gamma)\;d\gamma\;d\mu\\
&\quad=\int_0^{\mu_f}\Big[-\int_0^{\gamma_f}\frac{\partial}{\partial\gamma}\Big(h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\Big)\cdot\tilde\phi_k(\gamma)\;d\gamma\Big]\cdot\tilde\phi_j(\mu)\;d\mu\\
&\quad=\int_0^{\mu_f}\Big[-h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\tilde\phi_k(\gamma)\Big|_{\gamma=0}^{\gamma=\gamma_f}+\int_0^{\gamma_f}h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\tilde\phi_k'(\gamma)\;d\gamma\Big]\cdot\tilde\phi_j(\mu)\;d\mu\\
&\quad=\int_0^{\mu_f}\Big[-h_5(Fe_{pl},\gamma_f)P_5(t,\mu,\gamma_f)\tilde\phi_k(\gamma=\gamma_f)+h_5(Fe_{pl},0)P_5(t,\mu,0)\tilde\phi_k(\gamma=0)\\
&\qquad\qquad+\int_0^{\gamma_f}h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\tilde\phi_k'(\gamma)\;d\gamma\Big]\cdot\tilde\phi_j(\mu)\;d\mu\\
&\quad=\int_0^{\mu_f}\Big[-h_5(Fe_{pl},\gamma_f)P_5(t,\mu,\gamma_f)\phi_k(\gamma=\gamma_f)+\int_0^{\gamma_f}h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\tilde\phi_k'(\gamma)\;d\gamma\Big]\cdot\tilde\phi_j(\mu)\;d\mu,
\end{aligned}
$$

where we have applied boundary condition (49) and used the fact that $\tilde\phi_k(x)=\phi_k(x)$ when x is a nodal point. Substituting the approximate solution, we then obtain

$$
\begin{aligned}
&\int_0^{\mu_f}\Big[-h_5(Fe_{pl},\gamma_f)P_5^a(t,\mu,\gamma_f)\phi_k(\gamma=\gamma_f)+\int_0^{\gamma_f}h_5(Fe_{pl},\gamma)P_5^a(t,\mu,\gamma)\tilde\phi_k'(\gamma)\;d\gamma\Big]\cdot\tilde\phi_j(\mu)\;d\mu\\
&\quad=\int_0^{\mu_f}\Big[-h_5(Fe_{pl},\gamma_f)\Big(\sum_{\ell=1}^{N_\gamma}P_5^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\phi_\ell(\gamma=\gamma_f)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\phi_i(\mu)\phi_\ell(\gamma=\gamma_f)\Big)\phi_k(\gamma=\gamma_f)\\
&\qquad+\int_0^{\gamma_f}h_5(Fe_{pl},\gamma)\Big(\sum_{\ell=1}^{N_\gamma}P_5^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\phi_\ell(\gamma)+\sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma}A_{i,\ell}(t)\phi_i(\mu)\phi_\ell(\gamma)\Big)\tilde\phi_k'(\gamma)\;d\gamma\Big]\cdot\tilde\phi_j(\mu)\;d\mu
\end{aligned}
$$

$$
\begin{aligned}
&= \int_0^{\mu_f} \Bigg[- h_5(Fe_{pl},\gamma_f) P_5^{bdy,\mu}(t,\gamma_f)\phi_1(\mu)\phi_k(\gamma=\gamma_f) - h_5(Fe_{pl},\gamma_f)\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_i(\mu)\phi_k(\gamma=\gamma_f) \\
&\qquad + \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\phi_1(\mu)\cdot\Big[\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma\Big] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\phi_i(\mu)\cdot\Big[\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma\Big]\Bigg]\cdot\tilde{\phi}_j(\mu)\ d\mu \\
&= -h_5(Fe_{pl},\gamma_f)P_5^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu\Big] \\
&\qquad - h_5(Fe_{pl},\gamma_f)\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu\Big] \\
&\qquad + \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\tilde{\phi}_j(\mu)\ d\mu\Big]\cdot\Big[\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma\Big] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\tilde{\phi}_j(\mu)\ d\mu\Big]\cdot\Big[\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\tilde{\phi}_k'(\gamma)\ d\gamma\Big] \\
&= -h_5(Fe_{pl},\gamma_f)P_5^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\ d\mu\Big] \\
&\qquad - h_5(Fe_{pl},\gamma_f)\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\ d\mu + \omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\ d\mu\Big] \\
&\qquad + \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\Big[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\ d\mu\Big] \\
&\qquad\qquad \cdot\Big[\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma\Big] \\
&\qquad + \sum_{i=2}^{N_\mu}\sum_{\ell=1}^{N_\gamma} A_{i,\ell}(t)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\ d\mu + \omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\ d\mu\Big] \\
&\qquad\qquad \cdot\Big[\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma\Big]. \qquad (57)
\end{aligned}
$$

6.3.6 States Vectors and Linear ODEs

States vectors of the same form seen in (32) will be used to discretize the problem so that a linear system of ODEs of the form seen in (33) can be constructed for the class P_5 PDE.

6.3.7 Mass Matrix

The matrix M, which is called the mass matrix, will be constructed as

$$M = [M_1 + \omega_\mu M_2] \cdot * [M_3 + \omega_\gamma M_4],$$

where "$\cdot *$" denotes element-wise multiplication and the matrices M_1 through M_4 are defined based on the the four integrals in the last term of (54). Since these four integrals are identical to the four integrals in the last term of (27), M_1 through M_4 should be identical to the mass matrix components

described for class P_3, *except* that the values of N_μ, N_γ, h_μ, h_γ, ω_μ, and ω_γ corresponding to class P_5 should be used when constructing these matrices.

6.3.8 Stiffness Matrix

The matrix K, which is called the stiffness matrix, will be constructed as

$$K = K^{\text{VIII}} + K^{\text{IX}} + K^{\text{X}},$$

where components VIII though X are determined by contributions from equations (55) through (57), respectively.

The first component of the stiffness matrix is

$$K^{\text{VIII}} = -\left(K_1^{\text{VIII}} + \omega_\mu K_2^{\text{VIII}} + \omega_\gamma K_3^{\text{VIII}} + \omega_\mu\omega_\gamma K_4^{\text{VIII}}\right),$$

where the matrices K_1^{VIII} through K_4^{VIII} are defined based on the four integrals in the last term of (55). Note that each of these integrals involves the variable pair $E = (EPO, \frac{d}{dt}EPO)$ which is time-dependent, so the matrices K_1^{VIII} through K_4^{VIII} will need to be recomputed at each time step.

The matrix K_1^{VIII} consists of $(N_\mu - 1) \times (N_\mu - 1)$ blocks which we denote $B_{ji}^{(\text{VIII1})}$ (where each $B_{ji}^{(\text{VIII1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$), so

$$K_1^{\text{VIII}} = \begin{bmatrix} B_{1,1}^{(\text{VIII1})} & B_{1,2}^{(\text{VIII1})} & \cdots & B_{1,N_{\mu-1}}^{(\text{VIII1})} \\ B_{2,1}^{(\text{VIII1})} & B_{2,2}^{(\text{VIII1})} & \cdots & B_{2,N_{\mu-1}}^{(\text{VIII1})} \\ \vdots & \vdots & \ddots & \vdots \\ B_{N_{\mu-1},1}^{(\text{VIII1})} & B_{N_{\mu-1},2}^{(\text{VIII1})} & \cdots & B_{N_{\mu-1},N_{\mu-1}}^{(\text{VIII1})} \end{bmatrix}.$$

In this case, each block is different. The element of block $B_{j-1,i-1}^{(\text{VIII1})}$ at position (k, ℓ) is given by

$$\left[B_{j-1,i-1}^{(\text{VIII1})}\right]_{k\ell} = \int_0^{\mu_f}\int_0^{\gamma_f} \delta_5\left(\mu, \gamma, EPO, \frac{d}{dt}EPO\right) \phi_i(\mu)\phi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\; d\mu\; d\gamma,$$

where $i, j \in \{2, \ldots, N_\mu\}$ and $k, \ell \in \{1, \ldots, N_\gamma\}$.

The matrix K_2^{VIII} has the same structure and size as K_1^{VIII}, but the element of block $B_{j-1,i-1}^{(\text{VIII2})}$ at position (k, ℓ) is now given by

$$\left[B_{j-1,i-1}^{(\text{VIII2})}\right]_{k\ell} = \int_0^{\mu_f}\int_0^{\gamma_f} \delta_5\left(\mu, \gamma, EPO, \frac{d}{dt}EPO\right) \phi_i(\mu)\chi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\; d\mu\; d\gamma.$$

The matrix K_3^{VIII} also has the same structure and size as K_1^{VIII}, but the element of block $B_{j-1,i-1}^{(\text{VIII3})}$ at position (k, ℓ) is given by

$$\left[B_{j-1,i-1}^{(\text{VIII3})}\right]_{k\ell} = \int_0^{\mu_f}\int_0^{\gamma_f} \delta_5\left(\mu, \gamma, EPO, \frac{d}{dt}EPO\right) \phi_i(\mu)\phi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\; d\mu\; d\gamma.$$

Finally, the matrix K_4^{VIII} has the same structure and size as K_1^{VIII}, but the element of block $B_{j-1,i-1}^{(\text{VIII4})}$ at position (k, ℓ) is given by

$$\left[B_{j-1,i-1}^{(\text{VIII4})}\right]_{k\ell} = \int_0^{\mu_f}\int_0^{\gamma_f} \delta_5\left(\mu, \gamma, EPO, \frac{d}{dt}EPO\right) \phi_i(\mu)\chi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\; d\mu\; d\gamma.$$

The second component of the stiffness matrix is

$$K^{\mathrm{IX}} = \rho_5 \left[K_1^{\mathrm{IX}} + \omega_\mu K_2^{\mathrm{IX}}\right] \cdot * \left[K_3^{\mathrm{IX}} + \omega_\gamma K_4^{\mathrm{IX}}\right] - \rho_5 K_5^{\mathrm{IX}},$$

where "$\cdot *$" denotes element-wise multiplication, the matrices K_1^{IX} through K_4^{IX} are defined based on the four integrals in the last term of (56), and K_5^{IX} is defined based on the integrals in the first term of (56).

Since the four integrals in the last term of (56) are identical to the four integrals in the last term of (30), K_1^{IX} through K_4^{IX} should be identical to the matrices K_1^{III} through K_4^{III} described for class P_3, *except* that the values of N_μ, N_γ, h_μ, h_γ, ω_μ, and ω_γ corresponding to class P_5 should be used when constructing these matrices.

Since the integrals in the first term of (56) are identical to those in the first term of (30), K_5^{IX} should be identical to the matrix K_5^{III} described for class P_3, *except* that the values of N_μ, N_γ, h_μ, h_γ, ω_μ, and ω_γ corresponding to class P_5 should be used when constructing this matrix.

The third component of the stiffness matrix is

$$K^{\mathrm{X}} = \left[K_1^{\mathrm{X}} + \omega_\mu K_2^{\mathrm{X}}\right] \cdot * \left[K_3^{\mathrm{X}} + \omega_\gamma K_4^{\mathrm{X}}\right] - h_5(Fe_{pl}, \gamma_f) K_5^{\mathrm{X}},$$

where "$\cdot *$" denotes element-wise multiplication, the matrices K_1^{X} through K_4^{X} are defined based on the four integrals in the last term of (57), and K_5^{X} is defined based on the integrals in the second term of (57).

Since the first integral in the last term of (57) is identical to the first integral in the last term of (54), K_1^{X} should be identical to the mass matrix component M_1 for class P_5. Also, since the second integral in the last term of (57) is identical to the second integral in the last term of (54), K_2^{X} should be identical to the mass matrix component M_2 for class P_5.

The matrix K_3^{X} is made up of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks, which we will denote $B^{(\mathrm{X3})}$. We define

$$K_3^{\mathrm{X}} = \begin{bmatrix} B^{(\mathrm{X3})} & B^{(\mathrm{X3})} & \dots & B^{(\mathrm{X3})} \\ B^{(\mathrm{X3})} & B^{(\mathrm{X3})} & \dots & B^{(\mathrm{X3})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{X3})} & B^{(\mathrm{X3})} & \dots & B^{(\mathrm{X3})} \end{bmatrix},$$

where $B^{(\mathrm{X3})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ has entries given by

$$[B^{(\mathrm{X3})}]_{k\ell} = \int_0^{\gamma_f} h_5(Fe_{pl}, \gamma) \phi_\ell(\gamma) \phi_k'(\gamma)\, d\gamma.$$

The variable Fe_{pl} is time-dependent, so this subcomponent of K^{X} will have to be recomputed at each time step. If we let

$$f(\gamma) = h_5(Fe_{\mathrm{curr}}, \gamma), \tag{58}$$

where Fe_{curr} is the current value of Fe_{pl}, and then evaluate this function at the nodes we used to partition $[0, \gamma_f]$, we can approximate f using a piecewise linear interpolation. If we let $f_i = f(\gamma_i)$, then we can approximate the integral defining $[B^{(\mathrm{X3})}]_{k\ell}$ as

$$\int_0^{\gamma_f} f(\gamma) \phi_\ell(\gamma) \phi_k'(\gamma)\, d\gamma = \begin{cases} -\frac{1}{3} f_1 - \frac{1}{6} f_2 & \text{if } k = \ell = 1 \\ \frac{1}{6} f_{N_\gamma - 1} + \frac{1}{3} f_{N_\gamma} & \text{if } k = \ell = N_\gamma \\ \frac{1}{6} f_{k-1} - \frac{1}{6} f_{k+1} & \text{if } k = \ell \notin \{1, N_\gamma\} \\ \frac{1}{3} f_{k-1} + \frac{1}{6} f_k & \text{if } k - \ell = 1 \\ -\frac{1}{6} f_k - \frac{1}{3} f_{k+1} & \text{if } \ell - k = 1 \\ 0 & \text{otherwise.} \end{cases}$$

Thus, the identical blocks that make up K_3^{X} can be written

$$B^{(\mathrm{X3})} = \frac{1}{6}\begin{bmatrix} (-2f_1 - f_2) & (-f_1 - 2f_2) & 0 & \cdots & 0 \\ (2f_1 + f_2) & (f_1 - f_3) & (-f_2 - 2f_3) & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & \left(2f_{N_\gamma-2} + f_{N_\gamma-1}\right) & \left(f_{N_\gamma-2} - f_{N_\gamma}\right) & \left(-f_{N_\gamma-1} - 2f_{N_\gamma}\right) \\ 0 & \cdots & 0 & \left(2f_{N_\gamma-1} + f_{N_\gamma}\right) & \left(f_{N_\gamma-1} + 2f_{N_\gamma}\right) \end{bmatrix}.$$

The matrix K_4^{X} has the same form as K_3^{X} except that the block matrix $B^{(\mathrm{X4})}$ has entries given by

$$[B^{(\mathrm{X4})}]_{k\ell} = \int_0^{\gamma_f} h_5(Fe_{pl}, \gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma.$$

As with K_3^{X}, K_4^{X} must be recomputed at each time step because of its dependence on Fe_{pl}. If we once again let f be the function defined in (58) and let $f_i = f(\gamma_i)$, then we can approximate the integral defining $[B^{(\mathrm{X4})}]_{k\ell}$ as

$$\int_0^{\gamma_f} f(\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma = \begin{cases} -\frac{1}{6}f_k & \text{if } k = \ell = 1 \in \{1, N_\gamma\} \\ -\frac{1}{3}f_k & \text{if } k = \ell \notin \{1, N_\gamma\} \\ \frac{1}{6}f_{k-1} & \text{if } k - \ell = 1 \\ \frac{1}{6}f_{k+1} & \text{if } \ell - k = 1 \\ 0 & \text{otherwise.} \end{cases}$$

Thus, the identical blocks that make up K_4^{X} can be written

$$B^{(\mathrm{X4})} = \frac{1}{6}\begin{bmatrix} -f_1 & f_2 & 0 & \cdots & 0 \\ f_1 & -2f_2 & f_3 & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & f_{N_\gamma-2} & -2f_{N_\gamma-1} & f_{N_\gamma} \\ 0 & \cdots & 0 & f_{N_\gamma-1} & -f_{N_\gamma} \end{bmatrix}.$$

The matrix K_5^{X} consists of $(N_\mu - 1) \times (N_\mu - 1)$ *identical* blocks which we denote $B^{(\mathrm{X5})}$, so

$$K_5^{\mathrm{X}} = \begin{bmatrix} B^{(\mathrm{X5})} & B^{(\mathrm{X5})} & \cdots & B^{(\mathrm{X5})} \\ B^{(\mathrm{X5})} & B^{(\mathrm{X5})} & \cdots & B^{(\mathrm{X5})} \\ \vdots & \vdots & \ddots & \vdots \\ B^{(\mathrm{X5})} & B^{(\mathrm{X5})} & \cdots & B^{(\mathrm{X5})} \end{bmatrix}.$$

Note that the term responsible for generating this matrix is

$$\sum_{i=2}^{N_\mu} A_{i,N_\gamma}(t)\phi_k(\gamma=\gamma_f)\cdot\Big[\int_0^{\mu_f}\phi_i(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_i(\mu)\chi_j(\mu)\;d\mu\Big].$$

Because the only $A_{i,\ell}(t)$ terms that are present are those for which $\ell = N_\gamma$, and because $\phi_k(\gamma = \gamma_f)$ is only nonzero when $k = N_\gamma$, the only nonzero elements in this matrix are those corresponding to $k = \ell = N_\gamma$ (the lower right-hand element of each block.) Thus, if we define $D \in \mathbb{R}^{N_\gamma \times N_\gamma}$ as

$$D=\begin{bmatrix}0 & 0 & \cdots & 0\\ 0 & \ddots & \ddots & \vdots\\ \vdots & \ddots & 0 & 0\\ 0 & \cdots & 0 & 1\end{bmatrix},$$

then

$$K_5^{\mathrm{X}}=\begin{bmatrix}D & D & \cdots & D\\ D & D & \cdots & D\\ \vdots & \vdots & \ddots & \vdots\\ D & D & \cdots & D\end{bmatrix}\cdot *\left[M_1+\omega_\mu M_2\right],$$

where "$\cdot *$" denotes element-wise multiplication.

6.3.9 The Boundary Conditions Vector

The only item in (33) (for the class P_5 ODEs) which we have yet to describe is the vector b, which incorporates all contributions from the boundary conditions stated in (50). This vector will be constructed as

$$b = b^{\mathrm{X}} + b^{\mathrm{XI}} + b^{\mathrm{XII}} + b^{\mathrm{XIII}},$$

where components X though XIII are determined by contributions from equations (54) through (57), respectively.

The vector $b^{\mathrm{X}} \in \mathbb{R}^{(N_\mu-1)N_\gamma}$ is generated by the term

$$-\sum_{\ell=1}^{N_\gamma}\frac{\partial}{\partial t}P_5^{bdy,\mu}(t,\gamma_\ell)\cdot\left[\int_0^{\mu_f}\phi_1(\mu)\phi_j(\mu)\;d\mu+\omega_\mu\int_0^{\mu_f}\phi_1(\mu)\chi_j(\mu)\;d\mu\right]\cdot\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right]$$

in (54), where we have changed the sign to place the vector on the right-hand side of (33). This vector has the same block form as the states vectors described in (32), so $j \in \{2, \ldots, N_\mu\}$ indicates a specific block and $k \in \{1, \ldots, N\gamma\}$ indicates the position within that block. The expression in the first pair of brackets above is only nonzero for $j = 2$, so only entries in the first block of b^{X} are nonzero. Now if we consider the vector $\dot{v} \in \mathbb{R}^{N_\gamma}$ given by $\dot{v}_\ell = \frac{\partial}{\partial t}P_5^{bdy,\mu}(t, \gamma_\ell)$ and define a matrix $C^{(\mathrm{X})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\mathrm{X})}]_{k\ell}=\left[\int_0^{\gamma_f}\phi_\ell(\gamma)\phi_k(\gamma)\;d\gamma+\omega_\gamma\int_0^{\gamma_f}\phi_\ell(\gamma)\chi_k(\gamma)\;d\gamma\right],$$

then

$$b^{\mathrm{X}} = -\left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12}\right) \cdot \begin{bmatrix} C^{(\mathrm{X})}\dot{v} \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N^\gamma}$. Revisiting the derivation for the mass matrix components M_3 and M_4, it is clear that

$$C^{(\mathrm{X})} = B^{(3)} + \omega_\gamma B^{(4)}.$$

Observe that the expressions for $C^{(\mathrm{X})}$ and $C^{(\mathrm{I})}$ as well as the expressions for $b^{(\mathrm{X})}$ and $b^{(\mathrm{I})}$ are identical. However, the actual data structures may differ since here we must use values of N_μ, h_μ, and ω_μ corresponding to class P_5.

The vector $b^{\mathrm{XI}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ is generated by the term

$$\begin{aligned} -\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t, \gamma_\ell) \cdot \Bigg[&\Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_5(\mu, \gamma, E)\phi_1(\mu)\phi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\, d\mu\, d\gamma \Big) \\ &+ \omega_\mu \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_5(\mu, \gamma, E)\phi_1(\mu)\chi_j(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\, d\mu\, d\gamma \Big) \\ &+ \omega_\gamma \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_5(\mu, \gamma, E)\phi_1(\mu)\phi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\, d\mu\, d\gamma \Big) \\ &+ \omega_\mu\omega_\gamma \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_5(\mu, \gamma, E)\phi_1(\mu)\chi_j(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\, d\mu\, d\gamma \Big) \Bigg] \end{aligned}$$

in (55). This vector has the same block form as the states vectors described in (32), so $j \in \{2, \ldots, N_\mu\}$ indicates a specific block and $k \in \{1, \ldots, N\gamma\}$ indicates the position within that block. Since the expressions $\phi_1(\mu)\phi_j(\mu)$ and $\phi_1(\mu)\chi_j(\mu)$ are only nonzero for $j = 2$, only entries in the first block of b^{XI} are nonzero. Now, if we consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_5^{bdy,\mu}(t, \gamma_\ell)$ and define a matrix $C^{(\mathrm{XI})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$\begin{aligned} [C^{(\mathrm{XI})}]_{k\ell} = -\Bigg[&\Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_5 \left(\mu, \gamma, EPO, \frac{d}{dt}EPO\right) \phi_1(\mu)\phi_2(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\, d\mu\, d\gamma \Big) \\ &+ \omega_\mu \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_5 \left(\mu, \gamma, EPO, \frac{d}{dt}EPO\right) \phi_1(\mu)\chi_2(\mu)\phi_\ell(\gamma)\phi_k(\gamma)\, d\mu\, d\gamma \Big) \\ &+ \omega_\gamma \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_5 \left(\mu, \gamma, EPO, \frac{d}{dt}EPO\right) \phi_1(\mu)\phi_2(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\, d\mu\, d\gamma \Big) \\ &+ \omega_\mu\omega_\gamma \Big(\int_0^{\mu_f} \int_0^{\gamma_f} \delta_5 \left(\mu, \gamma, EPO, \frac{d}{dt}EPO\right) \phi_1(\mu)\chi_2(\mu)\phi_\ell(\gamma)\chi_k(\gamma)\, d\mu\, d\gamma \Big) \Bigg], \end{aligned}$$

then

$$b^{\mathrm{XI}} = \begin{bmatrix} C^{(\mathrm{XI})} v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N\gamma}$. Note that each of the integrals used to define $C^{(\mathrm{XI})}$ involves the variable pair $E = (EPO, \frac{d}{dt}EPO)$ which is time-dependent, so this matrix will need to be recomputed at each time step.

The vector $b^{\mathrm{XII}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ can be computed as

$$b^{\mathrm{XII}} = b_1^{\mathrm{XII}} + b_2^{\mathrm{XII}},$$

where b_1^{XII} is generated by the term

$$\rho_5 \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t, \gamma_\ell) \cdot \left[\int_0^{\mu_f} \phi_1(\mu)\phi_j'(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j'(\mu)\ d\mu \right] \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right]$$

in (56) and b_2^{XII} is generated by the term

$$\rho_5 \sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t, \gamma_\ell)\phi_j(\mu = 0) \cdot \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right],$$

also in (56). These vectors have the same block form as the states vectors described in (32), so $j \in \{2, \ldots, N_\mu\}$ indicates a specific block and $k \in \{1, \ldots, N\gamma\}$ indicates the position within that block.

Note that $\phi_1(\mu)\phi_j'(\mu)$ and $\phi_1(\mu)\chi_j'(\mu)$ are only nonzero for $j = 2$ and, so only entries in the first block of b_1^{XII} are nonzero. If we consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_5^{bdy,\mu}(t, \gamma_\ell)$ and define a matrix $C^{(\mathrm{XII1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\mathrm{XII1})}]_{k\ell} = \left[\int_0^{\gamma_f} \phi_\ell(\gamma)\phi_k(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} \phi_\ell(\gamma)\chi_k(\gamma)\ d\gamma \right],$$

then

$$b_1^{\mathrm{XII}} = \rho_5 \left(\frac{1}{2} + \frac{\omega_\mu}{6} \right) \cdot \begin{bmatrix} C^{(\mathrm{XII1})} v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0, \ldots, 0)^T \in \mathbb{R}^{N\gamma}$. Note that $C^{(\mathrm{XII1})} = C^{(\mathrm{X})}$. Also, note that $\phi_j(\mu = 0) = 0$ for all $j \in \{2, \ldots, N_\mu\}$, so $b_2^{\mathrm{XII}} = (0, \ldots, 0)^T$. Therefore, $b^{\mathrm{XII}} = b_1^{\mathrm{XII}}$.

The vector $b^{\text{XIII}} \in \mathbb{R}^{(N_\mu - 1)N_\gamma}$ can be computed as

$$b^{\text{XIII}} = b_1^{\text{XIII}} + b_2^{\text{XIII}},$$

where b_1^{XIII} is generated by the term

$$\sum_{\ell=1}^{N_\gamma} P_5^{bdy,\mu}(t,\gamma_\ell) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu \Big] \cdot \Big[\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma \Big]$$

in (57) and b_2^{XIII} is generated by the term

$$-h_5(Fe_{pl},\gamma_f)P_5^{bdy,\mu}(t,\gamma_f)\phi_k(\gamma=\gamma_f) \cdot \Big[\int_0^{\mu_f} \phi_1(\mu)\phi_j(\mu)\ d\mu + \omega_\mu \int_0^{\mu_f} \phi_1(\mu)\chi_j(\mu)\ d\mu \Big],$$

also in (57). These vectors have the same block form as the states vectors described in (32), so $j \in \{2,\dots,N_\mu\}$ indicates a specific block and $k \in \{1,\dots,N\gamma\}$ indicates the position within that block.

Note that $\phi_1(\mu)\phi_j(\mu)$ and $\phi_1(\mu)\chi_j(\mu)$ are only nonzero for $j = 2$ and, so only entries in the first block of b_1^{XIII} are nonzero. If we once again consider the vector $v \in \mathbb{R}^{N_\gamma}$ given by $v_\ell = P_5^{bdy,\mu}(t,\gamma_\ell)$ and define a matrix $C^{(\text{XIII1})} \in \mathbb{R}^{N_\gamma \times N_\gamma}$ with entries given by

$$[C^{(\text{XIII1})}]_{k\ell} = \left[\int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\phi_k'(\gamma)\ d\gamma + \omega_\gamma \int_0^{\gamma_f} h_5(Fe_{pl},\gamma)\phi_\ell(\gamma)\chi_k'(\gamma)\ d\gamma \right],$$

then

$$b_1^{\text{XIII}} = \left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12} \right) \cdot \begin{bmatrix} C^{(\text{XIII1})}v \\ \hline 0 \\ \hline \vdots \\ \hline 0 \end{bmatrix},$$

where each 0 represents the vector $(0,\dots,0)^T \in \mathbb{R}^{N^\gamma}$. Because the variable Fe_{pl} is time-dependent, the matrix $C^{(\text{XIII1})}$ will have to be recomputed at each time step. If we let f be the function defined in (58) and let $f_i = f(\gamma_i)$, then we can approximate the integral defining $[C^{(\text{XIII1})}]_{k\ell}$ as was done for $[B^{(\text{X3})}]_{k\ell}$ and $[B^{(\text{X4})}]_{k\ell}$. In fact,

$$C^{(\text{XIII1})} = B^{(\text{X3})} + \omega_\gamma B^{(\text{X4})}.$$

For the vector b_2^{XIII}, note again that the integrals in the brackets are only nonzero for $j = 2$. Also, because $\phi_k(\gamma = \gamma_f)$ is only nonzero when $k = N_\gamma$, the only nonzero element in this vector is

the last element of the first block. In fact,

$$b_2^{\text{XIII}} = -h_5(Fe_{pl}, \gamma_f) P_5^{bdy,\mu}(t, \gamma_f) \left(\frac{h_\mu}{6} + \omega_\mu \frac{h_\mu}{12} \right) \cdot \left[\begin{array}{c} 0 \\ \vdots \\ 0 \\ 1 \\ \hline 0 \\ \vdots \\ 0 \\ \hline \vdots \\ \hline 0 \\ \vdots \\ 0 \end{array} \right].$$

6.3.10 Testing Numerical Solver for Class $\mathbf{P}_5$ PDE

To test the numerical solution technique described above, we once again apply the method of synthetic solutions. To begin, we append a forcing term to the PDE given in (12) to obtain the new PDE

$$\begin{aligned} \frac{\partial}{\partial t}\tilde{P}_5(t,\mu,\gamma) = &-\delta_5 \left(\mu, \gamma, EPO, \frac{d}{dt}EPO \right) \tilde{P}_5(t,\mu,\gamma) - \rho_5 \frac{\partial}{\partial \mu}\tilde{P}_5(t,\mu,\gamma) \\ &- \frac{\partial}{\partial \gamma}\left[h_5(Fe_{pl},\gamma)\tilde{P}_5(t,\mu,\gamma) \right] + f(t,\mu,\gamma). \end{aligned} \tag{59}$$

Next, we select our "known solution" to be

$$\tilde{P}_5(t,\mu,\gamma) = \left(\sin\frac{2\pi t}{3} + 2 \right) \cdot \left(\frac{\mu}{\mu_f} + 1 \right) \cdot \left(e^{\gamma/\gamma_f} - 1 \right).$$

This solution was chosen to have a temporal period of 3 days since the solver can generate solutions for that period in a reasonable amount of time. Solving (59) for $f(t,\mu,\gamma)$ and then substituting in the known solution, we obtain

$$\begin{aligned} f(t,\mu,\gamma) = &\frac{\partial}{\partial t}\tilde{P}_5(t,\mu,\gamma) + \delta_5(\mu,\gamma,EPO,\frac{d}{dt}EPO)\tilde{P}_5(t,\mu,\gamma) + \rho_5\frac{\partial}{\partial \mu}\tilde{P}_5(t,\mu,\gamma) \\ &+ \frac{\partial}{\partial \gamma}\left[h_5(Fe_{pl},\gamma)\tilde{P}_5(t,\mu,\gamma) \right] \end{aligned}$$

$$
\begin{aligned}
f(t,\mu,\gamma) = &\left(\frac{2\pi}{3}\cos\frac{2\pi t}{3}\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right)\\
&+\delta_5(\mu,\gamma,EPO,\frac{d}{dt}EPO)\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right)\\
&+\rho_5\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{1}{\mu_f}\right)\left(e^{\gamma/\gamma_f}-1\right)\\
&+\left[\frac{\partial}{\partial\gamma}h_5(Fe_{pl},\gamma)\right]\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right)\\
&+h_5(Fe_{pl},\gamma)\left(\sin\frac{2\pi t}{3}+2\right)\left(\frac{\mu}{\mu_f}+1\right)\left(\frac{1}{\gamma_f}e^{\gamma/\gamma_f}\right).
\end{aligned}
$$

Now, the weak form for the class P_5 PDE becomes

$$
\begin{aligned}
&\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial t}P_5(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 1]}\\
&\quad=-\int_0^{\mu_f}\int_0^{\gamma_f}\delta_5\left(\mu,\gamma,EPO,\frac{d}{dt}EPO\right)P_5(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 2]}\\
&\quad\quad-\rho_5\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\mu}P_5(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 3]}\\
&\quad\quad-\int_0^{\mu_f}\int_0^{\gamma_f}\frac{\partial}{\partial\gamma}\Big(h_5(Fe_{pl},\gamma)P_5(t,\mu,\gamma)\Big)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Term 4]}\\
&\quad\quad+\int_0^{\mu_f}\int_0^{\gamma_f}f(t,\mu,\gamma)\cdot\tilde{\phi}_j(\mu)\cdot\tilde{\phi}_k(\gamma)\;d\gamma\;d\mu \quad \text{[Forcing Term]}.
\end{aligned}
$$

Thus, the ODE for the row corresponding to each (j,k) in (33) will have an additional "forcing term". These additional terms force the numerical solver to return the desired solution $\tilde{P}_5(t,\mu,\gamma)$. Note that the initial conditions must be set to

$$
\tilde{P}_5(0,\mu,\gamma)=P_5^{init}(\mu,\gamma)=2\left(\frac{\mu}{\mu_f}+1\right)\left(e^{\gamma/\gamma_f}-1\right)
$$

and the $\mu=0$ boundary conditions must be set to

$$
\tilde{P}_5(t,0,\gamma)=\tilde{P}_5^{bdy,\mu}(t,\gamma)=\left(\sin\frac{2\pi t}{3}+2\right)\cdot\left(e^{\gamma/\gamma_f}-1\right)
$$

when using this validation technique.

6.4 Numerical Solution of Iron States ODEs Coupled with PDEs for Classes $\mathbf{P}_3$ through $\mathbf{P}_5$

Recall that the state variables included in the iron compartment are H, Fe_{re}, Fe_{li}, and Fe_{pl}. The dynamics of these variables are described by the coupled system of ODEs given by (17), (18), (19), and (20) and their associated initial conditions. This system of ODEs is easily solved using any numerical ODE solver (e.g., MATLAB's `ode23`), but note that the equations depend on the RBC lineage states P_3, P_4, and P_5 (and vice-versa). Therefore, the discretized ODE systems for the RBC states (described in the preceding sections) must be coupled with the iron compartment ODEs to construct one large system of ODEs. Given solutions for EPO, P_1, and P_2, and a set of initial conditions for the remaining states, this large ODE system can be solved using a numerical ODE solver.

7 Results

We have implemented the numerical scheme described in the preceding sections as a collection of MATLAB codes, and in the sections that follow we describe the results we have observed when applying these codes to various hypothetical scenarios. As we have yet to obtain real experimental data with which to compare the output of our model, we can only comment on the qualitative behavior observed in these simulations. We begin by describing some of our model validation experiments, and then discuss simulation results for a set of increasingly complex scenarios.

7.1 Validation of Independent Solvers

In order to validate the numerical schemes presented in Section 6, we began by implementing independent versions of the solvers described for classes P_3, P_4, and P_5, and conducted the tests described in Sections 6.1.10, 6.2.10, and 6.2.10. These tests were performed with course meshes (on the structure variables), and then the meshes were systematically refined. The numerical solutions in each case were observed to converge to the correct "synthetic" solutions.

7.2 Simulations with Unlimited Iron

To begin with a relatively simple scenario, we attempted to simulate an artificial environment in which an unlimited amount of iron was available to the RBC lineage cells. This was accomplished by initializing the Fe_{pl}, the iron level in the blood plasma, to a level of 500 mg and removing the code affecting the dynamics of this state variable such that the right hand side of (20) was effectively zero. Also, the states Fe_{re}, Fe_{li}, and H were removed from consideration. The first group of videos in the files that accompany this document show the outcome of this experiment. It should be noted that all simulations in this group were conducted using $(\mu_5)_f = 3$ days (rather than 100 days) in order to allow for more reasonable execution times of the simulation code. For all classes and all simulations in this group, step sizes of $h_\mu = 0.1$ and $h_\gamma = 0.1$ were used. Also, numerical solutions for $P_2(t, \mu_2)$ and $EPO(t)$ with periods of 3 days were used as input. Such solutions correspond to an "every-third-day" (ETD) treatment protocol.

The first video in this group shows the behavior of cells in classes P_3, P_4, and P_5 during 3 simulated days. We start from an initial condition in which the distribution of cells with respect to iron level is constant across all maturity levels and all classes. From this starting point, we observe that the peaks in the density surfaces rapidly move in the positive γ direction; that is, the cells in all three classes rapidly begin acquiring iron. This is to be expected given the unlimited iron supply.

The next two videos show the behavior of the the behavior of the same cells during two subsequent periods (days 3-9 and days 9-15, respectively). These videos show that the system reaches a dynamic equilibrium with period 3 days. The undulations that can be seen in the density surfaces after the system reaches this equilibrium may be attributed to affects of the EPO level and the boundary condition (7), which depends on the state of class P_2. Recall that both $EPO(t)$ and $P_2(t, \mu_2)$ are periodic with respect to time t.

In all of these simulations, it may be observed that the functions P_3, P_4, and P_5 take on negative values at some points. As these functions represent densities, such values are physically impossible. We assume that this is a numerical effect that could be corrected by refining the mesh (i.e., by using smaller values of h_μ and h_γ. Unfortunately, such refinement leads to prohibitively long execution times with the current implementation of our numerical scheme. More will be said about such limitations of our numerical implementation later in Section 7.5.

7.3 Simulations with a Single Iron State Variable

Next, we added a level of complexity to our simulations by allowing for some dynamics in the Fe_{pl} state. In particular, we created a closed system in which iron was not unlimited, but flowed between Fe_{pl} and the RBC lineage states. Note that this can be effected by modifying (20) such that the right hand side includes one positive term incorporating iron lost by classes P_3, P_4, and P_5 due to cell deaths, and one negative term incorporating iron taken up by these same classes via the process of hemoglobinization.

In the second group of videos in the accompanying files, we show the results of 18 days of simulations in which a single iron state variable (Fe_{pl}) is accounted for, and the parameter $k_{Fe,eff}$ is set to 10. Recall from (15) that this parameter affects the rate at which iron can be taken up by the RBC lineage cells. As with the previous experiments, we limited $(\mu_5)_f$ to 3 days (rather than 100) and used step sizes of $h_\mu = 0.1$ and $h_\gamma = 0.1$. Similarly, we continued to use as input numerical solutions for $P_2(t, \mu_2)$ and $EPO(t)$ with periods of 3 days. We used the final states of the previous group of experiments as initial conditions for this set of experiments.

The videos depicting the results of these experiments show that the RBC states proceed according to the previously established dynamic equilibrium until approximately day 3. At this point the blood plasma iron level drops below a critical threshold, and the RBCs begin to lose iron. After a few more simulation days, a new dynamic equilibrium is established and the blood plasma iron level oscillates between about 7.5 and 8.5 mg according to a three-day period prescribed by the input functions.

In the third group of videos on the RESULTS SITE, we show the results of 12 days of simulations with a single iron state variable and the parameter $k_{Fe,eff}$ set to 20. We used the final states of the previous group of experiments as initial conditions for this set of experiments, and otherwise left the parameters and inputs unchanged. This group of videos shows that doubling the value of $k_{Fe,eff}$ led to a new dynamic equilibrium in which the mean value for the blood plasma iron level was approximately half of its previous mean level. The amplitude of the blood plasma level oscillations was also approximately halved.

In the fourth group of videos, we show the results of 6 simulated days in which the entire relevant field of class P_5 states are considered. That is, we set $(\mu_5)_f$ back to the more appropriate value (according to the literature) of 100 days. In order to allow the numerical solver to complete these simulations in a reasonable amount of time, we set the h_μ step size for class P_5 to the rather large value 1 day. Even after 27 simulated days, we were unable to find a dynamic equilibrium for the system. It is likely that the large value of h_μ was responsible for this failure. Nevertheless, the simulation results seemed to indicate that densities in class P_5 are essentially negligible beyond 25-30 days of maturity (at least for the parameter values we considered).

This last realization led us to perform the experiments depicted in the fifth group of videos. In this group, we used all the same parameters and inputs described for the fourth group, but we changed $(\mu_5)_f$ to 25 days and set the h_μ step size for class P_5 to the more numerically reasonable value of 0.1 days. This led to the largest numerical problems of all those we considered, and each of the "six-day" simulations depicted in this group of videos required approximately 60 hours to complete. Viewing these videos, one notices that a dynamic equilibrium is almost achieved, but there is a net iron loss occurring over time. Close inspection of the class P_5 states indicates that our truncation at 25 days may have been too extreme. That is, some cells, and therefore some iron, appear to be flowing out of the system at the $\mu_5 = 25$ boundary of the spatial domain for the P_5 states.

To test our hypothesis that the truncation of the class P_5 domain was responsible for the net iron loss we observed, we conducted the same experiment described above, but let $(\mu_5)_f = 30$. The simulation results for this experiment are depicted in the last video, which is grouped by itself. Here,

we still see a net loss of iron in the system, but the net loss is less (50 mg versus 80 mg). So we conclude that we need to increase the size of the class P_5 domain yet again.

7.4 Future Simulations

The overall goal of the simulations described above is to establish a viable set of initial conditions with which we can run simulations in order to observe the qualitative behavior of the complete system (including all cells in the RBC lineage, Hepcidin, EPO, and the various iron states. To this end, the next steps should be (1) to establish dynamic equilibrium for the system by finding an appropriate value of $(\mu_5)_f$ (apparently greater than 30), (2) incorporate the H (hepcidin) state and establish a dynamic equilibrium for the system, (3) incorporate the two remaining iron states and establish a dynamic equilibrium for the system, and finally (4) analyze and discuss the overall qualitative behavior of the complete system.

7.5 Limitations of Current Implementation

As we have mentioned in the foregoing discussion, our implementation requires computation times on the order of days for even fairly course spatial grids. In order to make more precise simulations feasible, the numerical scheme discussed in this paper would need to be recoded using a low-level (compiled) language, such as C or C++. Completion of this task and the acquisition of experimental data might make it possible to consider statistical methods for parameter estimation (inverse problems), but with the current implementation it would be futile to consider such an undertaking. The results presented here serve merely as a proof-of-concept for the applications of our model and numerical scheme.

8 Summary

We have developed a model for both red blood cell and iron dynamics in patients in ESRD receiving periodic treatments of exogenous iron and EPO. In particular, our model consists of PDEs governing RBCs and their progenitors (Equations (3)-(12)) coupled with ODEs governing EPO and iron levels (Equations (16)-(20)), along with appropriate initial and boundary conditions. We use structure variables to account for the maturity and iron endowment of cells in the red blood cell lineage. The model also permits investigation of the effects of neocytolysis and inflammation on red blood cell dynamics. We describe a scheme for obtaining numerical solutions for the resulting system of coupled PDEs and ODEs and discuss simulation results. These results demonstrate that our model is capable of reproducing reasonable qualitative behavior for the system in question.

Acknowledgments:

This research was supported in part by the National Institute of Allergy and Infectious Disease (under grant NIAID 9R01AI071915) and in part by the National Science Foundation (under Research Training Group (RTG) grant DMS-0636590 and Research Experience for Early Graduate Students (REG) grant DMS-0943855).

References

[1] Plasma hepcidin levels are elevated but responsive to erythropoietin therapy in renal disease, *Kidney International*, **75** (2009), 976–981.

[2] A. Ackleh, K. Deng, K. Ito, and J. Thibodeaux, A structured erythropoiesis model with nonlinear cell maturation velocity and hormone decay rate, *Mathematical Biosciences*, **204** (206), 21–48.

[3] Clarence P. Alfrey and Stephen Fishbane, Implications of neocytolysis for optimal management of anemia in chronic kidney disease, *Nephron Clinical Practice*, **106** (2007), c149–c156.

[4] Clarence P. Alfrey, Mark M. Udden, Carolyn Leach-Huntoon, Theda Driscoll, and Mark H. Pickett, Control of red blood cell mass in spaceflight, *Journal of Applied Physiology*, **81** (1996), 98–104.

[5] H. T. Banks, Karen M. Bliss, Peter Kotanko, and Hien Tran, A computational model of red blood cell dynamics in patients with chronic kidney disease, CRSC Tech Report TR11-03, N.C. State University, Raleigh, NC, February, 2011.

[6] H. T. Banks, Karen M. Bliss, and H. T. Tran, Modeling red blood cell and iron dynamics in patients with chronic kidney disease, *International Journal of Pure and Applied Mathematics*, **103** (2012), 103–140.

[7] H. T. Banks, C. Cole, P. Schlosser, and H. T. Tran, Modeling and optimal regulation of erythropoiesis subject to benzene intoxication, *Mathematical Biosciences and Engineering*, **1** (2004), 15–48.

[8] J. Belair, M. Mackey, and J. Mahaffy, Age-structured and two-delay models for erythropoiesis, *Mathematical Biosciences*, **128** (1995), 317–346.

[9] Karen M. Bliss. *Modeling of Red Blood Cell Dynamics in Patients with Chronic Kidney Disease*, Ph D Thesis, N. C. State University, Raleigh, NC, May, 2011.

[10] Francesco M. Van Bockxmeer and Evan H. Morgan, Transferrin receptors during rabbit reticulocyte maturation, *Biochemica et Biophysica Acta*, **584** (1979), 76–83.

[11] Robert T. Card and Lewis R. Weintraub, Metabolic abnormalities of erythrocytes in severe iron deficiency, *Blood*, **37** (1971), 725–732.

[12] Chung-Che Chang, Yayan Chen, Kapil Modi, Omar Awar, Clarence P. Alfrey, and Lawrence Rice, Changes of red blood cell surface markers in a blood doping model of neocytolysis, *Journal of Investigative Medicine*, **57** (2009), 650–654.

[13] Stefan N. Constantinescu, Mechanism of erythropoietin receptor activation, In S. G. Elliot, M. A. Foote, and G. Molineaux, editors, *Erythropoietins, Erythropoietic Factors and Erythropoiesis*, Birkhauser Verlag/Switzerland, 2009, pp. 175–196.

[14] Maria Diez-Ewald and Miguel Layrisse, Mechanisms of hemolysis in iron deficiency anemia: further studies, *Blood*, **32** (1968), 884–894.

[15] Z. Farid, J. H. Nichols, S. Bassily, and A. R. Schulert, Blood loss in pure *Ancylostoma Duodenale* infection in egyptian farmers, *American Journal of Tropical Medicine and Hygiene*, **14** (1965), 375–378.

[16] Janet L. Frazier, Jennifer H. Caskey, Mark Yoffe, and Paul A. Seligman, Studies of the transferrin receptor on both human reticulocytes and nucleated human cells in culture, *Journal of Clinical Investigation*, **69** (1982), 853–865.

[17] Tomas Ganz, Iron homeostasis: Fitting the puzzle pieces together, *Cell Metabolism*, **7** (2008), 288–290.

[18] John P. Greer, John Foerster, George M. Rodgers, Frixos Paraskevas, Bertil Glader, Daniel A. Arber, and Jr. Robert T. Means, *Wintrobe's Clinical Hematology*, Lippincott Williams and Wilkins, 12th edition, 2009.

[19] Connie J. Gregory and Allen C. Eaves, Human marrow cells capable of erythropoietic differentiation in vitro: definition of three erythroid colony responses, *Blood*, **49** (1977), 855–864.

[20] Connie J. Gregory and Allen C. Eaves, Three stages of erythropoietic progenitor cell differentiation distinguished by a number of physical and biologic properties, *Blood*, **51** (1978), 527–537.

[21] L. Israels and E. Israels, Erythropoiesis: an overview, In *Erythropoietins and Erythropoiesis: Molecular, Cellular, Preclinical and Clinical Biology*, Birkhäuser Verlag, 2003.

[22] W. Jelkmann, Erythropoietin: structure, control of production, and function, *Physiol Rev.*, **72** (1992), 449–489.

[23] Mark J. Koury and Prem Ponka, New insights in erythropoiesis: The roles of Folate, Vitamin B12, and Iron, *Annual Review of Nutrition*, **24** (2004), 105–131.

[24] Sanford B. Krantz, Erythropoietin, *Blood*, **77** (1991), 419–434.

[25] Joseph Ly, Rosa Marticorena, and Sandra Donnelly, Red blood cell survival in chronic renal failure, *American Journal of Kidney Diseases*, **44** (2004), 715–719.

[26] I. Macdougall, Use of recombinant erythropoietins in the setting of renal disease, In S.G. Elliot G. Molineaux, M.A. Foote, eds., *Erythropoietins and Erythropoiesis: Molecular, Cellular, Preclinical and Clinical Biology*, Birkhäuser Verlag, 2003, pp. 153–159.

[27] I. Macdougall and A. Cooper, Erythropoietin resistance: the role of inflammation and pro-inflammatory cytokines, *Nephrol. Dial. Transplant.*, **17** (2002), 39–43.

[28] J. Mahaffy, J. Belair, and M. Mackey, Hematopoietic model with moving boundary condition and state dependent delay: applications in erythropoiesis, *Journal of Theoretical Biology*, **190** (1998), 135-146.

[29] Cesar F. Merino, Studies on blood formation and destruction in the polycythemia of high altitude, *Blood*, **5** (1950), 1–31.

[30] National Kidney Foundation Kidney Disease Outcomes Quality Initiative, KDOQI Clinical Practice Guidline and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease: 2007 Update of Hemoglobin Target, *American Journal of Kidney Diseases*, **50** (2007), 471–530.

[31] Elizabeta Nemeth and Tomas Ganz, The role of hepcidin in iron metabolism, *Acta Haematologica*, **122** (2009), 78–86.

[32] R. Ramakrishnan, W. Cheung, M. Wacholtz, N. Minton, and W. Jusko, Pharmacokinetic and pharmacodynamic modeling of human erythropoietin after single and multiple doses in healthy volunteers, *The Journal of Clinical Pharmacology*, **44** (2004), 991–1002.

[33] Lawrence Rice and Clarence Alfrey, The negative regulation of red cell mass by neocytolysis: Physiologic and pathophysiologic manifestations, *Cellular Physiology and Biochemistry*, **15** (2005), 245–250.

[34] Lawrence Rice, Clarence P. Alfrey, Theda Driscoll, Carl E. Whitley, David L. Hachey, and Wadi Suki, Neocytolysis contributes to the anemia of renal disease, *American Journal of Kidney Disease*, **33** (1999), 59–62.

[35] Lawrence Rice, Wilson Rulz, Theda Driscoll, Carl E. Whitley, Rosario Tapia, David L. Hachey, Gustavo F. Gonzales, and Clarence P. Alfrey, Neocytolysis on descent from altitude: A newly recognized mechanism for the control of red cell mass, *Annals of Internal Medicine*, **134** (2001), 652–656.

[36] Bernadette F. Rodak, George A. Fritsma, and Kathryn Doig], *Hematology: Clinical Principles and Applications*, Saunders Elsevier, 3rd ed, 2007.

[37] Pradeep Sathyanarayana, Arvind Dev, Jing Fang, Estelle Houde, Olga Bogacheva, Oleg Bogachev, Madhu Menon, Sarah Browne, Anamika Pradeep, Christine Emerson, and Don M. Wojchowski, Epo receptor circuits for primary erythroblast survival, *Blood*, **111** (2008), 5390–5399.

[38] K. Sawada, S. B. Krantz, S-H. Dai, S. T. Koury, S. T. Horn, A. D. Glick, and C. I. Civin, Purification of human blood burst-forming units-erythroid and demonstration of the evolution of erythropoietin receptors, *Journal of Cellular Physiology*, **142** (1990), 219–230.

[39] K. Sawada, S. B. Krantz, J. S. Kans, E. N. Dessypris, S. Sawyer, A. D. Glick, and C. I. Civin, Purification of human erythroid colony-forming units and demonstration of specific binding of erythropoietin, *Journal of Clinical Investigation*, **80** (1987), 357–366.

[40] A. B. Shaw, Haemolysis in chronic renal failure, *British Medical Journal*, **2** (1967), 213–216.

[41] A. Simmons, *Basic Hematology*, Charles C Thomas, Springfield, Illinois, 1973.

[42] J. H. Stewart, Haemolytic anemia in acute and chronic renal failure, *QJM*, **36** (1967), 85–105.

[43] U.S. Renal Data System, *USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008.

[44] M. M. Udden, T. B. Driscoll, M. H. Pickett, C. S. Leach-Huntoon, and C. P. Alfrey, Decreased production of red blood cells in human subjects exposed to microgravity, *Journal of Laboratory and Clinical Medicine*, **125** (1995), 442–449.

[45] M. C. Verloop, M. Van der Wolk, and A. J. Heier, Radioactive iron studies in patients with iron deficiency anemia with concurrent abnormal hemolysis, *Blood*, **15** (1960), 791–806.

[46] Mark Westerman, Gordana Olbina, Vaughn Ostland, Elizabeta Nemeth, and Tomas Ganz, Hepcidin: An emerging biomarker for iron disorders, inflammatory diseases, and infections, *Proceedings of SPIE*, **7666** (2010), 766617-1.

[47] S. Woo, W. Krzyzanski, and W. Jusko, Pharmacokinetic and pharmacodynamic modeling of recombinant human erythropoietin after intravenous and subcutaneous administration in rats, *Journal of Pharmacology and Experimental Therapeutics*, **319** (2006), 1297–1306.

[48] Hong Wu, Xin Liu, Rudolf Jaenisch, and Harvey F. Lodish, Generation of committed erythroid bfu-e and cfu-e progenitors does not require erythropoietin or the erythropoietin receptor, *Cell*, **83** (1995), 59–67.