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ADAPTIVE TIME-STEPPING FOR CAHN-HILLIARD-TYPE EQUATIONS WITH APPLICATION TO DIFFUSE-INTERFACE TUMOR-GROWTH MODELS

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Abstract. Many tumor-growth phenomena can be considered as multiphase problems. Employing the continuum theory of mixtures, phase-field tumor-growth models can be derived with diffuse interfaces. The chosen form of the Helmholtz free-energy leads to equations of the Cahn-Hilliard type. Such nonlinear fourth-order partial-differential equations are time-dependent, and their solutions exhibit alternating fast and slow variations in time. It is therefore of prime importance to use adaptive time-stepping to efficiently simulate the entire dynamics of the system [5].
In this contribution, we consider a thermodynamically consistent four-species model of tumor growth in which the energy is non-increasing and total mass is conserved [6]. In order to inherit these two main characteristics of the system at the discrete level, we propose a gradient-stable time-stepping scheme with second-order accuracy [8]. Mixed finite elements are used for spatial discretization. For this discretization, we discuss various adaptive time-stepping strategies in time. Furthermore, we present illustrative numerical results.

1 INTRODUCTION: DIFFUSE-INTERFACE TUMOR-GROWTH MODEL

We consider the diffuse-interface tumor-growth model proposed in Hawkins-Daarud, van der Zee and Oden [6] of the form:

find (u, μ_u, n, μ_n) such that

$$\begin{aligned}
u_t &= \Delta\mu_u + P(u)(\mu_n - \mu_u) && \text{for } (x,t) \in \Omega \times (0,T] \\
\mu_u &= -\epsilon^2 \Delta u + \Psi'(u) && \text{for } (x,t) \in \Omega \times (0,T] \\
n_t &= \Delta\mu_n - P(u)(\mu_n - \mu_u) && \text{for } (x,t) \in \Omega \times (0,T] \\
\mu_n &= \frac{n}{\delta} && \text{for } (x,t) \in \Omega \times (0,T] \\
\nabla u \cdot \boldsymbol{n} &= \nabla\mu_u \cdot \boldsymbol{n} \;=\; \nabla\mu_n \cdot \boldsymbol{n} \;=\; 0 && \text{for } x \in \partial\Omega \times (0,T] \\
u(x,0) &= u_0, \quad n(x,0) = n_0 && \text{for } x \in \Omega
\end{aligned}$$

where u represents the phase of *tumor* and at the same time serves to model the interface, n denotes the phase of *nutrients*, μ_u and μ_n are the chemical potentials corresponding to u and n, respectively, and $P(u) \geq 0$ is a nonnegative *proliferation* function defined as

$$P(u) := \begin{cases} \delta\hat{P}(1-u^2) & u \in [-1,1] \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

with $\delta > 0$ and $\hat{P} \geq 0$. It is assumed that the domain Ω is a bounded subset of $\mathbb{R}^d$ with $d = 1, 2$ or 3, with Lipschitz boundary $\partial\Omega$. For the sake of simplicity we consider natural boundary conditions, and constant mobility and diffusion (equal to 1). Furthermore, we do not consider chemotaxis; see [6] for details on chemotaxis.

The nonlinear free-energy density function $\Psi(u)$ is a double well potential. We consider the following $C^{2,1}$-continuous Ψ:

$$\Psi(u) := \begin{cases} (u+1)^2 & u < -1 \\ \dfrac{1}{4}(u^2-1)^2 & u \in [-1,1] \\ (u-1)^2 & u > 1 \end{cases} \tag{2}$$

Notice that when $\hat{P} = 0$, the system decouples in a Cahn-Hilliard and a diffusion equation.

2 ENERGY DISSIPATION AND MASS CONSERVATION

The total free energy of the tumor-growth model is defined as

$$E(u,n) := \int_\Omega \left(\frac{\epsilon^2}{2}|\nabla u|^2 + \Psi(u) + \frac{1}{2\delta}n^2 \right) \tag{3}$$

Similar to the Cahn–Hilliard equation, the tumor-growth model dissipates the total free energy:

$$\frac{\mathrm{d}}{\mathrm{d}t}E(u(t),n(t)) = -\|\nabla\mu_u\|^2 - \|\nabla\mu_n\|^2 - \int_\Omega P(u)(\mu_n - \mu_u)^2 \leq 0$$

which is proved in [6]. Furthermore, the total "mass" is conserved, i.e.

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega (u+n)\ d\boldsymbol{x} = \int_\Omega (\Delta\mu_u + \Delta\mu_n) d\boldsymbol{x} = \int_{\partial\Omega} (\nabla\mu_u \cdot \boldsymbol{n} + \nabla\mu_n \cdot \boldsymbol{n}) dS = 0$$

where we employed the homogeneous Neumann boundary conditions.

3 SECOND-ORDER ACCURATE SCHEME

Many problems of interest in the physical and engineering sciences require the understanding of dynamical features which evolve over long-time periods. However, most of standard time-stepping schemes are conditionally energy stable in the sense that the free energy is dissipated at the discrete level only for small enough time steps. This stability issue is the motivation for a large amount of literature on the development of schemes that are provably energy-stable.

Here, we focus on the time-discretization. Therefore we present our ideas without discretizing in space. Of course, one may obtain fully discrete schemes by using finite-difference of finite-element methods in space.

Elliott and Stuart [2, Eq. (5.4)] and Eyre [4] proposed a first-order accurate unconditional energy-stable scheme for gradient-flow systems based on the splitting of E into a convex (contractive) and concave (expansive) part, i.e.

$$E = E_c - E_e$$

where both E_c and E_e are convex.

Following the same idea of energy splitting, we propose in [8] a unconditionally energy-stable second-order time-accurate schemes for the tumor-growth model as follows:

$$\frac{u_{k+1}-u_k}{\tau} = \Delta\tilde{\mu}_u + \tilde{P}_{k+1/2}(\tilde{\mu}_n - \tilde{\mu}_u) \tag{4a}$$

$$\tilde{\mu}_u = \tilde{\Psi}'(u_k, u_{k+1}) - \epsilon^2\Delta\frac{u_{k+1}+u_k}{2} - \alpha_1\tau\Delta(u_{k+1}-u_k) + \alpha_2\tau(u_{k+1}-u_k) \tag{4b}$$

$$\frac{n_{k+1}-n_k}{\tau} = \Delta\tilde{\mu}_n - \tilde{P}_{k+1/2}(\tilde{\mu}_n - \tilde{\mu}_u) \tag{4c}$$

$$\tilde{\mu}_n = \frac{n_{k+1}+n_k}{2\delta} \tag{4d}$$

where

$$\tilde{P}_{k+1/2} := P\left(\frac{3}{2}u_k - \frac{1}{2}u_{k-1}\right) \tag{5}$$

$$\tilde{\Psi}'(u_k, u_{k+1}) = \Psi'_{c,k+1} - \frac{u_{k+1}-u_k}{2}\Psi''_{c,k+1} - \Psi'_{e,k} - \frac{u_{k+1}-u_k}{2}\Psi''_{e,k} \tag{6}$$

This scheme is a modification of the Crank-Nicolson method which includes splitting, stabilization and extrapolation. In particular $\tilde{\Psi}'(u_k, u_{k+1})$ is a novel second-order accurate

splitting employing an implicit Taylor expansion of the convex part Ψ_c' and an explicit Taylor expansion of the concave part Ψ_e'. The α_1-stabilization is an artificial diffusivitiy, while the α_2-stabilization can be thought of as *artificial convexity*. Furthermore, we apply the extrapolation technique for the treatment of $P(u)$, which allows the scheme to be linear (for quadratic $\Psi_c(u)$). The initial step of the scheme done by setting $u_{-1} = u_0$.

We summarize the properties of the above scheme in the following theorem, whose proof can be found in [8].

Theorem: Let the free energy density Ψ be $C^{2,1}$-continuous and have a convex splitting $\Psi = \Psi_c - \Psi_e$ with $C^{2,1}$-continuous Ψ_c and Ψ_e and finite second derivatives, i.e., $|\Psi_c''| \leq L_c$ and $|\Psi_e''| \leq L_e$ for some constants $L_c, L_e \geq 0$. Let the proliferation function P be $C^{0,1}$-continuous and satisfy $0 \leq P \leq \bar{P}$. If the stabilization is large enough, i.e. $\alpha_1 \geq (L_c + L_e)^2/16$ and $\alpha_2 \geq \bar{P}(L_c + L_e)^2/16$, then the time-stepping scheme (4) has the following properties:

1. Unconditional energy-stability: $E(u_{k+1}, n_{k+1}) \leq E(u_k, n_k)$
2. Total mass conservation: $\int_\Omega (u_{k+1} + n_{k+1}) d\boldsymbol{x} = \int_\Omega (u_0 + n_0) d\boldsymbol{x}$
3. Second-order accuracy.

Remark: Variable mobilities can also be considered in the tumor-growth model. If they are treated by extrapolation similar to [8], then this theorem also holds, but with the constraint:

$$\alpha_1 \geq \bar{M}(L_c + L_e)^2/16$$

4 ADAPTIVE TIME-STEPPING

In our talk we will consider various adaptive time-stepping strategies: a classical indicator, a comparison indicator and a goal-oriented indicator:

- Classical indicator: $\|u_{k+1} - u_k\| \leq TOL$
  The classical adaptive method has been studied and discussed by Johnson in [7], and extended in the context of parabolic problems by Eriksson et al in [3]. The indicator is based on the a posteriori error estimate in [3], controlling the size of the Galerkin discretization error.

- Comparison indicator: $\|u_{k+1}^{1st} - u_{k+1}^{2nd}\| \leq TOL$
  Based on the optimal a priori error estimates for a class of one-step methods, the idea of the comparison with a higher order method has been discussed by Johnson in [7]. The adaptive strategy is to compare the result between our second-order accurate scheme and the first order accurate scheme in [6]. If the value of the indicators is larger than some tolerance, we refine the time step size.

- Goal-oriented indicator
  A blockwise adaptive approach using adjoint solutions for time-dependent problems has been developed by Carey et al in [1]. Here, we will apply the same idea to time adaptvity, and develop the adjoint-based estimator for the tumor-growth model. Since energy-dissipation is of significant importance, this is selected as our quantity of interest.

We demonstrate that, in various cases, the computing time is reduced by more than one order of magnitude compared to constant time steps.

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