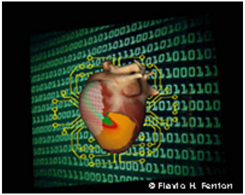
Two examples of coping with small parameters: time-stepping for Markov chains, and propagation in thin layers

T. Stary, I. V. Biktasheva, H. Dierckx and Vadim N. Biktashev



1. Time stepping for (ODE) Markov chain models (T.Stary, V.N. Biktashev, IEEE TBME 62: 1070–1076, 2015)
2. Wave propagation in thin layers (I.V. Biktasheva, H. Dierckx, V.N. Biktashev, PRL 114:068302, 2015)
3. Appendix: details of variable thickness asymptotics

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Cellular Membrane

Cellular membrane potential governed by equation:

$$\frac{\mathrm{d}V_m}{\mathrm{d}t} = \frac{1}{C_m}\left[I_{\mathrm{stim}}(t) - \sum_{k=1}^{N} I_k(V_m, \vec{X}, P_{\mathrm{open}})\right] \tag{1}$$

- V_m – membrane potential
- C_m – membrane capacitance
- $I_{\mathrm{stim}}(t)$ – external stimulation current
- $I_k(V_m, \vec{X}, P_{\mathrm{open}})$ – specific ion current
- $\vec{X}(t)$ – ionic concentrations

Ion Channel (1/2)

From the Ohm's law:

$$I_k = G_k P_{\text{open}}(t)[V_m(t) - E_k(X_k)] \tag{2}$$

- G_k – maximum conductance of specific ion current
- $E_k(X_k)$ – equilibrium voltage for specific ion (Nerst potential)
- $P_{\text{open}}(t)$ – open probability defined by one of the following ion channel models:
  - Gate model
  - Markov chain model

Ion Channel (2/2)

- Gate model – Hodgkin, Huxley (1952)

$$\frac{\mathrm{d}y_i}{\mathrm{d}t} = \alpha_{yi}(V_m)(1 - y_i) - \beta_{yi}(V_m)y_i \tag{3}$$

$$P_{\mathrm{open}}(t) = \prod_{i=1}^{N} y_i(t) \tag{4}$$

where y_i represent "gates" (hypothetical channel protein subunits); transition rates ($\alpha_{yi}(V_m)$, $\beta_{yi}(V_m)$) are found experimentally.

- Markov chain model

$$\frac{\mathrm{d}\vec{u}}{\mathrm{d}t} = \boldsymbol{A}(V_m)\vec{u} \tag{5}$$

$$P_{\mathrm{open}}(t) = u_1(t) \tag{6}$$

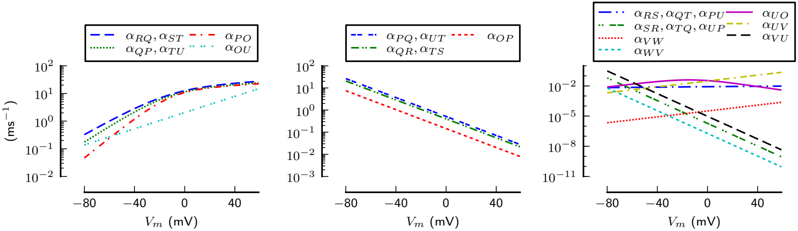
where u_1 is open (conductive) state; and transition rates matrix ($\boldsymbol{A}(V_m)$) is determined experimentally.

Sodium Channel Markov Chain (1/2)

$$
\begin{tikzcd}
S \arrow[r, shift left, "\alpha_{ST}"] \arrow[d, shift left, "\alpha_{SR}"] & T \arrow[l, shift left, "\alpha_{TS}"] \arrow[r, shift left, "\alpha_{TU}"] \arrow[d, shift left, "\alpha_{TQ}"] & U \arrow[l, shift left, "\alpha_{UT}"] \arrow[r, shift left, "\alpha_{UV}"] \arrow[d, shift left, "\alpha_{UP}"] \arrow[dr, shift left, "\alpha_{UO}"] & V \arrow[l, shift left, "\alpha_{VU}"] \arrow[r, shift left, "\alpha_{VW}"] & W \arrow[l, shift left, "\alpha_{WV}"] \\
R \arrow[u, shift left, "\alpha_{RS}"] \arrow[r, shift left, "\alpha_{RQ}"] & Q \arrow[u, shift left, "\alpha_{QT}"] \arrow[l, shift left, "\alpha_{QR}"] \arrow[r, shift left, "\alpha_{QP}"] & P \arrow[u, shift left, "\alpha_{PU}"] \arrow[l, shift left, "\alpha_{PQ}"] \arrow[r, shift left, "\alpha_{PO}"] & O \arrow[l, shift left, "\alpha_{OP}"] \arrow[ul, shift left, "\alpha_{OU}"] &
\end{tikzcd}
$$

I_{Na} Markov chain model: 9 interconnected dynamical states, state O denotes to conductive open state (u_1).

Standard	Our
O	O
C_1	P
C_2	Q
C_3	R
IC_3	S
IC_2	T
IF	U
IM_1	V
IM_2	W



Transition rates in the range of physiological potentials.

Sodium Channel Markov Chain (2/2)

$$
\begin{tikzcd}
S \arrow[r, shift left, "\alpha_{ST}"] \arrow[d, shift left, "\alpha_{SR}"] & T \arrow[l, shift left, "\alpha_{TS}"] \arrow[r, shift left, "\alpha_{TU}"] \arrow[d, shift left, "\alpha_{TQ}"] & U \arrow[l, shift left, "\alpha_{UT}"] \arrow[r, shift left, "\alpha_{UV}"] \arrow[d, shift left, "\alpha_{UP}"] \arrow[dr, shift left, "\alpha_{UO}"] & V \arrow[l, shift left, "\alpha_{VU}"] \arrow[r, shift left, "\alpha_{VW}"] & W \arrow[l, shift left, "\alpha_{WV}"] \\
R \arrow[u, shift left, "\alpha_{RS}"] \arrow[r, shift left, "\alpha_{RQ}"] & Q \arrow[l, shift left, "\alpha_{QR}"] \arrow[u, shift left, "\alpha_{QT}"] \arrow[r, shift left, "\alpha_{QP}"] & P \arrow[l, shift left, "\alpha_{PQ}"] \arrow[u, shift left, "\alpha_{PU}"] \arrow[r, shift left, "\alpha_{PO}"] & O \arrow[l, shift left, "\alpha_{OP}"] \arrow[ul, shift left, "\alpha_{OU}"]
\end{tikzcd}
$$

$$
\begin{aligned}
\frac{\mathrm{d}O}{\mathrm{d}t} &= \alpha_{PO}P + \alpha_{UO}U - (\alpha_{OP} + \alpha_{OU})O \\
\frac{\mathrm{d}P}{\mathrm{d}t} &= \alpha_{QP}Q + \alpha_{UP}U + \alpha_{OP}O - (\alpha_{PQ} + \alpha_{PU} + \alpha_{PO})P \\
\frac{\mathrm{d}Q}{\mathrm{d}t} &= \alpha_{RQ}R + \alpha_{TQ}T + \alpha_{PQ}P - (\alpha_{QR} + \alpha_{QT} + \alpha_{QP})Q \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \alpha_{SR}S + \alpha_{QR}Q - (\alpha_{RS} + \alpha_{RQ})R \\
\frac{\mathrm{d}S}{\mathrm{d}t} &= \alpha_{TS}T + \alpha_{RS}R - (\alpha_{ST} + \alpha_{SR})S \\
\frac{\mathrm{d}T}{\mathrm{d}t} &= \alpha_{QT}Q + \alpha_{ST}S + \alpha_{UT}U - (\alpha_{TQ} + \alpha_{TS} + \alpha_{TU})T \\
\frac{\mathrm{d}U}{\mathrm{d}t} &= \alpha_{TU}T + \alpha_{PU}P + \alpha_{VU}V + \alpha_{OU}O - (\alpha_{UT} + \alpha_{UP} + \alpha_{UO} + \alpha_{UV})U \\
\frac{\mathrm{d}V}{\mathrm{d}t} &= \alpha_{UV}U + \alpha_{WV}W - (\alpha_{VU} + \alpha_{VW})V \\
\frac{\mathrm{d}W}{\mathrm{d}t} &= \alpha_{VW}V - \alpha_{WV}W
\end{aligned}
$$

Reminder: Forward Euler (FE) method

For a given Markov Chain model $\mathrm{d}\vec{u}/\mathrm{d}t = \boldsymbol{A}(V_m(t))\vec{u}$, the forward Euler scheme reads

$$\vec{u}^{n+1} = [1 + h\,\boldsymbol{A}(V_m(t_n))]\,\vec{u}^n \tag{7}$$

where $h = t_{n+1} - t_n$ is the time step.

Numerical Instability Issues

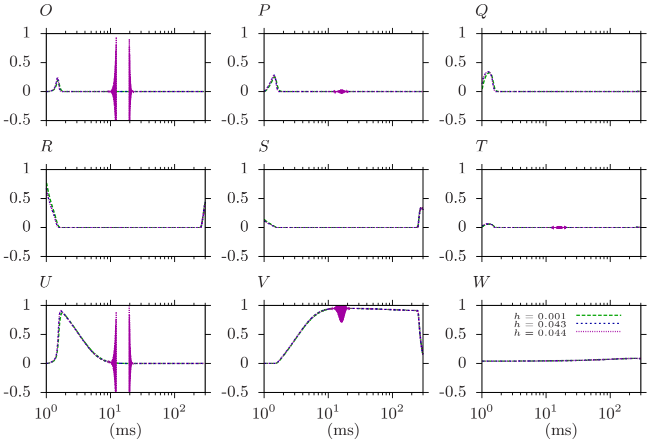


Figure: MC I_{Na} ion channel simulation driven by Action potential (V_m) at time step $h = 0.001, 0.043$ and 0.044 ms.

Fast-Slow approach to Markov chain (1/2)

$$\frac{\mathrm{d}\vec{u}}{\mathrm{d}t} = \left(\frac{1}{\epsilon} \boldsymbol{A}_f(V_m) + \boldsymbol{A}_s(V_m) \right) \vec{u}$$

E.g.

$$\hat{A}_f = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & * & \overrightarrow{TS} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \overrightarrow{ST} & * & \overrightarrow{UT} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \overrightarrow{TU} & * & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad \hat{A}_s = \begin{bmatrix} * & \overrightarrow{PO} & 0 & 0 & 0 & 0 & \overrightarrow{UO} & 0 & 0 \\ \overrightarrow{OP} & * & \overrightarrow{QP} & 0 & 0 & 0 & \overrightarrow{UP} & 0 & 0 \\ 0 & \overrightarrow{PQ} & * & \overrightarrow{RQ} & 0 & \overrightarrow{TQ} & 0 & 0 & 0 \\ 0 & 0 & \overrightarrow{QR} & * & \overrightarrow{SR} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \overrightarrow{RS} & * & 0 & 0 & 0 & 0 \\ 0 & 0 & \overrightarrow{QT} & 0 & 0 & * & 0 & 0 & 0 \\ \overrightarrow{OU} & \overrightarrow{PU} & 0 & 0 & 0 & 0 & * & \overrightarrow{VU} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \overrightarrow{UV} & * & \overrightarrow{WV} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \overrightarrow{VW} & * \end{bmatrix}$$

Fast-Slow approach to Markov chain (2/2)

$$
\begin{tikzcd}
S \arrow[r, shift left, "\alpha_{ST}"] \arrow[d, shift left, "\alpha_{SR}"] & T \arrow[l, shift left, "\alpha_{TS}"] \arrow[r, shift left, "\alpha_{TU}"] \arrow[d, shift left, "\alpha_{TQ}"] & U \arrow[l, shift left, "\alpha_{UT}"] \arrow[r, shift left, "\alpha_{UV}"] \arrow[d, shift left, "\alpha_{UN}"] & V \arrow[l, shift left, "\alpha_{VU}"] \arrow[r, shift left, "\alpha_{VW}"] & W \arrow[l, shift left, "\alpha_{WV}"] \\
R \arrow[u, shift left, "\alpha_{RS}"] \arrow[r, shift left, "\alpha_{RQ}"] & Q \arrow[u, shift left, "\alpha_{QT}"] \arrow[l, shift left, "\alpha_{QR}"] \arrow[r, shift left, "\alpha_{QN}"] & N \arrow[u, shift left, "\alpha_{NU}"] \arrow[l, shift left, "\alpha_{NQ}"] & &
\end{tikzcd}
$$

$$\Downarrow$$

$$
\begin{tikzcd}
R \arrow[r, shift left, "\alpha_{RM}"] \arrow[d, shift left, "\alpha_{RQ}"] & M \arrow[l, shift left, "\alpha_{MR}"] \arrow[r, shift left, "\alpha_{MV}"] \arrow[dl, shift left, "\alpha_{MQ}"] \arrow[d, shift left, "\alpha_{MP}"] \arrow[dr, shift left, "\alpha_{MO}"] & V \arrow[l, shift left, "\alpha_{VM}"] \arrow[r, shift left, "\alpha_{VW}"] & W \arrow[l, shift left, "\alpha_{WV}"] \\
Q \arrow[u, shift left, "\alpha_{QR}"] \arrow[ur, shift left, "\alpha_{QM}"] \arrow[r, shift left, "\alpha_{QP}"] & P \arrow[u, shift left, "\alpha_{PM}"] \arrow[l, shift left, "\alpha_{PQ}"] \arrow[r, shift left, "\alpha_{PO}"] & O \arrow[ul, shift left, "\alpha_{OM}"] \arrow[l, shift left, "\alpha_{OP}"] &
\end{tikzcd}
$$

Accuracy OK, but stability no better, for any plausible choice of “fast rates”: T. Stary, V.N. Biktashev, Chaos, 27: 093937 (2017)

Exponential Time Differentiation – Rush, Larsen (1978)

The exponential time differentiation scheme developed by Rush and Larsen (1978) is very popular for solving gate models of the form

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \alpha(V_m)(1-y) - \beta(V_m)y. \tag{8}$$

Considering $\alpha(V_m)$ and $\beta(V_m)$ constants *for the duration of one time step*, $V_m(t) \approx V_m(t^n)$, we can obtain analytical solution:

$$y^{n+1} = y_\infty(V_m) - [y_\infty(V_m) - y^n]\exp(-h/\tau) \tag{9}$$

where

- $y_\infty(V_m) = \alpha(V_m)/[\alpha(V_m) + \beta(V_m)]$ – "steady-state" solution
- $\tau = 1/[\alpha(V_m) + \beta(V_m)]$ – "time constant"
- $h = t_{n+1} - t_n$ – time step
- $y^n = y(t_n)$

Matrix Rush-Larsen (MRL)

We can extend the exponential time differentiation for a given Markov chain $\mathrm{d}\vec{u}/\mathrm{d}t = \boldsymbol{A}(V_m(t))\vec{u}$ as:

$$\vec{u}^{n+1} = \exp\left[\boldsymbol{A}(V_m(t_n))h\right]\vec{u}^n = \boldsymbol{T}(V_m)\vec{u}^n \tag{10}$$

Let $\boldsymbol{A}(V_m)$ be diagonalizable, so $\boldsymbol{A}(V_m) = \boldsymbol{S}(V_m)\boldsymbol{\Lambda}(V_m)\boldsymbol{S}(V_m)^{-1}$, where the columns of matrix $\boldsymbol{S}(V_m)$ are the eigenvectors of $\boldsymbol{A}(V_m)$ and matrix $\boldsymbol{\Lambda}(V_m)$ is diagonal with eigenvalues of $\boldsymbol{A}(V_m)$ in the corresponding places. Then matrix $\boldsymbol{T}$ can be computed as

$$\begin{aligned}\boldsymbol{T} &= \exp(\boldsymbol{A}h) = \sum_{j=0}^{\infty}\frac{(\boldsymbol{A}h)^j}{j!} = \sum_{j=0}^{\infty}\frac{(\boldsymbol{S\Lambda S}^{-1})^j h^j}{j!} = \sum_{j=0}^{\infty}\frac{(\boldsymbol{S\Lambda S}^{-1}\boldsymbol{S\Lambda S}^{-1}\dots\boldsymbol{S\Lambda S}^{-1})h^j}{j!} = \\ &= \boldsymbol{S}\left(\sum_{j=0}^{\infty}\frac{(\boldsymbol{\Lambda}h)^j}{j!}\right)\boldsymbol{S}^{-1} = \boldsymbol{S}\exp(\boldsymbol{\Lambda}h)\boldsymbol{S}^{-1}\end{aligned} \tag{11}$$

Tabulation (tab.)

Because finding eigenvalues and eigenvectors is computationally expensive,

- At/before compile time, we pre-compute the matrices $\boldsymbol{S}(\tilde{V}_m^j)$ and $\boldsymbol{\Lambda}(\tilde{V}_m^j)$, for a fine grid of physiological potentials: $\tilde{V}_m^j = -100 + 0.01j$, $j \in J = \{0, 1, \dots, j_{\max}\}$, $\tilde{V}_m^j \leq 70$ mV;
- At start time, we pre-compute, for given h,
  $\boldsymbol{T}^j = \boldsymbol{T}\left(\tilde{V}_m^j\right) = \boldsymbol{S}\left(\tilde{V}_m^j\right) \exp\left[\boldsymbol{\Lambda}\left(\tilde{V}_m^j\right) h\right] \boldsymbol{S}\left(\tilde{V}_m^j\right)^{-1}, j \in J$;
- At run time,

$$\vec{u}^{n+1} = \boldsymbol{T}^{j(n)} \vec{u}^{n} \tag{12}$$

where $j(n)$ is found from $\tilde{V}_m^{j(n)} \approx V_m(t_n)$.

NB: $\boldsymbol{T}^j$ are full (dense) matrices.

Results (1/2)

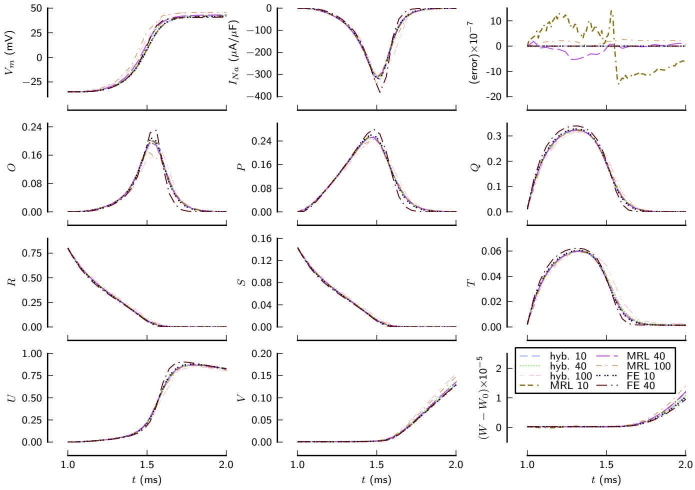


Figure: Cardiac excitation simulations with I_{Na} Markov chain model.

Results (2/2)

Table: Computational cost [s] during 100 pulses with cycle length of 1 s.

I_{Na} scheme	$\Delta t = 10\ \mu s$		$\Delta t = 40\ \mu s$		$\Delta t = 100\ \mu s$	
	I_{Na}	Total	I_{Na}	Total	I_{Na}	Total
FE (tab.)	2.48	19.98	0.60	5.01		
MRL (tab.)	2.96	20.45	0.74	5.16	0.28	2.06

Full model: C.E. Clancy and Y.Rudy, "Na^+ channel mutation that causes both Brugada and long-QT syndrome phenotypes: a simulation study of mechanism," *Circulation*, **105**:1208–1213 (2002).

Conclusions

The Matrix Rush-Larsen method:

- Resolves the stability issues, allowing large time steps, limited by stability of other parts of the model.
- Is first-order accurate as much as dependence on the control variable (e.g. V_m) is concerned.
- When tabulated, is comparable to Forward Euler in computing cost.
- Requires some start-up time (seconds) for building transition matrix.
- Is implemented in `BeatBox` distributed under GNU General Public Licence.

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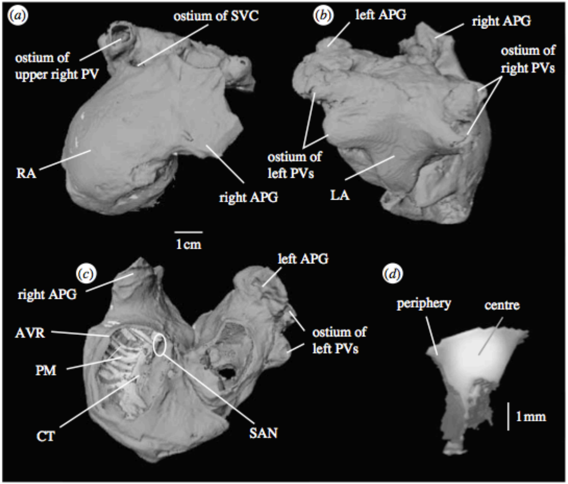
2. Wave propagation in thin layers (I.V. Biktasheva, H. Dierckx, V.N. Biktashev, PRL 114:068302, 2015)
3. Appendix: details of variable thickness asymptotics

Human atrium geometry

G. Seemann *et al.* "Heterogeneous three-dimensional anatomical and electrophysiological model of human atria", *Phil. Trans. Roy. Soc. A*, **364**(1843):1465–1481, 2006

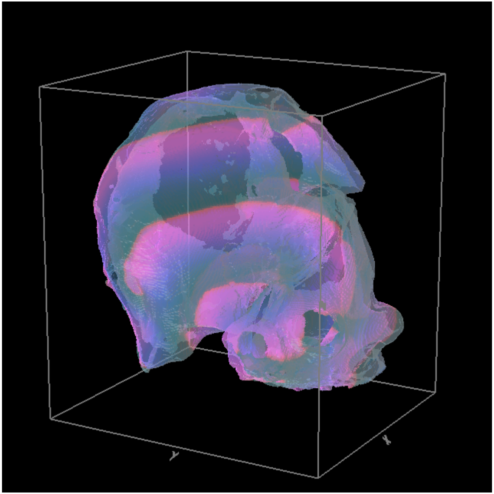


Spiral wave or scroll wave?

- Human heart atrium geometry: is it three-dimensional or two-dimensional?

A variant of Courtemanche at al. 1998 model

S.R. Kharche *et al.* "A Computer Simulation Study of Anatomy Induced Drift of Spiral Waves in the Human Atrium", *BioMed Research International*, 2015: 731386 (2015)

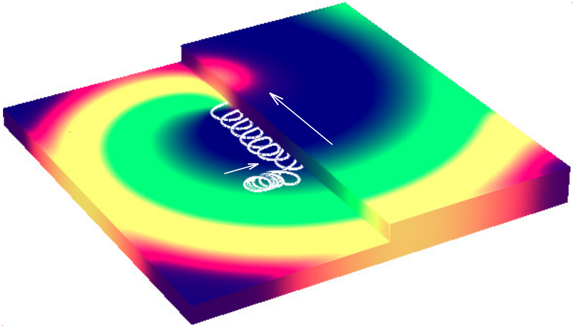


see movies

Drift near a step in thickness

- Not filament tension.
- Not surface curvature.
- What is it?

(FitzHugh-Nagumo system)

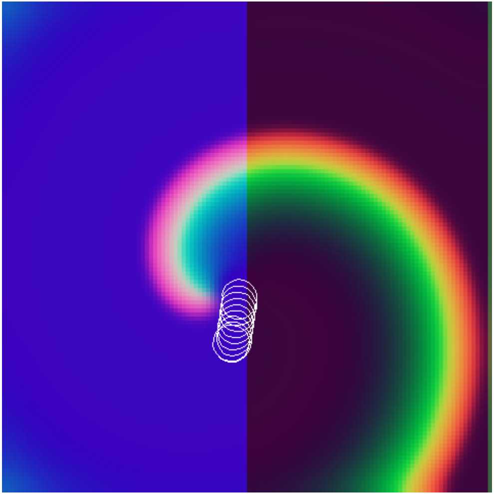


I.V. Biktasheva *et al.* "Drift of scroll waves in thin layers caused by thickness features: asymptotic theory and numerical simulations", *Phys. Rev. Lett.*, **114**: 068302, 2015

Drift near a step in thickness

- One of parameters varies stepwise in space
- This produces drifts that looks similar to that from thickness step
- Is this superficial or essential?

(FitzHugh-Nagumo system)



Reaction-diffusion systems in 2D

Generic:

$$\partial_t \mathbf{u} = \mathbf{f}(\mathbf{u}) + \mathbf{D}\nabla^2 \mathbf{u} + \epsilon \mathbf{h},$$

$$\mathbf{u}(\vec{r}, t), \mathbf{f}(\mathbf{u}), \mathbf{h}(\cdot) \in \mathbb{R}^{\ell},\ \mathbf{D} \in \mathbb{R}^{\ell \times \ell},\ \ell \geq 2,\ \vec{r} \in \mathbb{R}^2.$$

Here $\epsilon \mathbf{h}(\dots)$ is a perturbation of any kind, as long as it is small; mathematically, we consider $\epsilon \to 0$.

E.g., FitzHugh-Nagumo archetypical excitable model:

$$\begin{aligned}
\partial_t u &= \alpha^{-1}(u - u^3/3 - v) + \nabla^2 u + \epsilon h_u(\dots), \\
\partial_t v &= \alpha\,(u + \beta - \gamma v) + \epsilon h_v(\dots), \\
\alpha &= 0.3, \quad \beta = 0.68, \quad \gamma = 0.5.
\end{aligned}$$

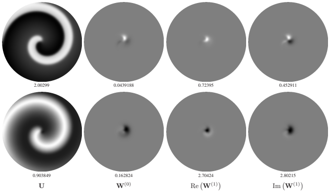
Spiral waves drift: equation of motion

- Drift velocity due to perturbation:

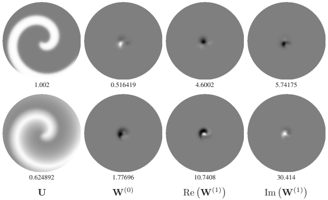
$$\dot{R} \approx \epsilon \int\limits_{\phi-\pi}^{\phi+\pi} \frac{\mathrm{e}^{-i\xi}}{2\pi} \iint\limits_{\mathbb{R}^2} \mathbf{W}_1{}^{+}(\mathbf{U};\rho,\theta)\tilde{\mathbf{h}}(\mathbf{U};\rho,\theta,\xi)\rho\,\mathrm{d}\rho\,\mathrm{d}\theta\,\mathrm{d}\xi$$

  where $R = X + \mathrm{i}Y \in \mathbb{C}$ is the complex coordinate of the position of the instant spiral rotation centre, (ρ,θ) are corotating polar coords, $\phi = \omega t - \Phi(t)$.
- (Translational) response function $\mathbf{W}_1(\rho,\theta) \in \mathbb{C}$: how infinitesimal perturbation at a certain point in space and certain moment in time affects the position of the spiral in the long run.
- Linear expressions, hence superposition principle.

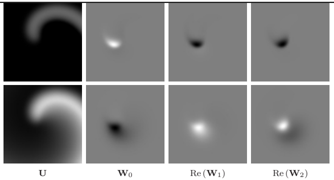
Spiral waves drift: why do the integrals converge



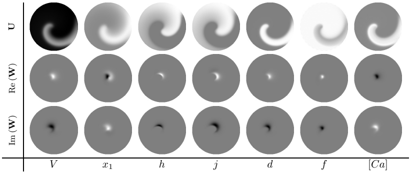
FitzHugh-Nagumo



Barkley

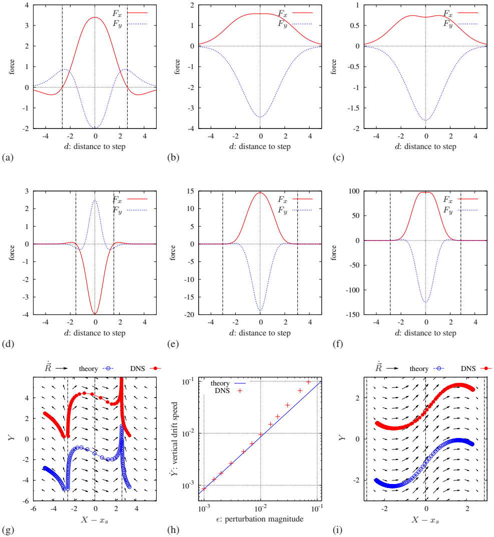


Oregonator
(BZ reaction)



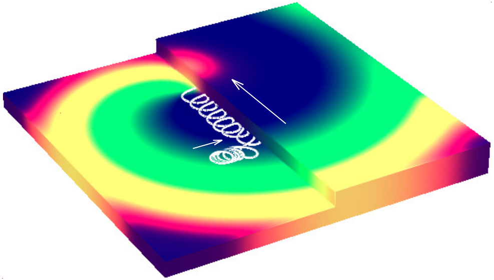
Beeler-Reuter
(heart ventricles)

Interaction with a parametric step



HOWEVER!

- Scroll wave, not spiral wave.
- Scroll wave asymptotics also available, but complicated, and doubtful to explain this phenomena.
- Can 2D theory help to describe the 3D effect?
- Need a 3D $\rightarrow$ 2D reduction!



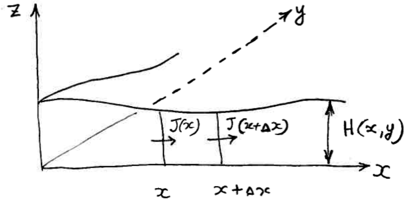
3D $\to$ 2D reduction for thin layers: the idea

$$\mathbf{v}_t = \mathbf{f}(\mathbf{v}) + \mathbf{D}\Delta_3\mathbf{v}, \qquad \mathbf{v} = \mathbf{v}(x,y,z,t)$$
$$(x,y)\in\mathbb{R}^2, \qquad 0\le z\le H(x,y) = \mu\tilde{H}(x,y), \qquad \mu \ll 1.$$

with no-flux boundaries at $z = z_{\text{min}}$ and $z = z_{\text{max}}$. Then

$$\mathbf{v}(x,y,z,t) = \mathbf{u}(x,y,t) + \mathcal{O}(\mu),$$

and

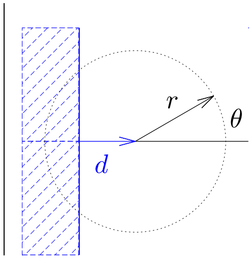


$$\mathbf{u}_t = \mathbf{f}(\mathbf{u}) + \mathbf{D}\frac{1}{H(x,y)}\nabla_2\cdot(H(x,y)\nabla_2\mathbf{u}) + \mathcal{O}(\mu^2)$$
$$\approx \mathbf{f}(\mathbf{u}) + \mathbf{D}\Delta_2\mathbf{u} + \mathbf{D}(\nabla_2(\ln H)\cdot\nabla_2\mathbf{u}), \qquad \epsilon\sim\ln H \ll 1$$

Attachment and drift near a step: interaction force

$$\frac{\mathrm{d}\vec{R}}{\mathrm{d}t} = \epsilon \vec{F}(\vec{R}) = \epsilon\,(F_x, F_y) = \epsilon \int_0^\infty \oint \mathbf{W}\,(r,\theta)^\dagger\, \boldsymbol{\alpha}(r,\theta;\vec{R})\,\mathrm{d}\theta\, r\mathrm{d}r,$$

$$\boldsymbol{\alpha}(r,\theta;\vec{R}) = \begin{cases} 0, & r \le |d|, \\ \dfrac{\mathbf{D}\mathrm{e}^{-\mathrm{i}\theta}}{\pi\sqrt{r^2-d^2}} \left[\dfrac{d^2}{r^2}\,\mathbf{U}_r - \dfrac{\mathrm{i}(r^2-d^2)}{r^3}\,\mathbf{U}_\theta\right] & r > |d|. \end{cases},$$

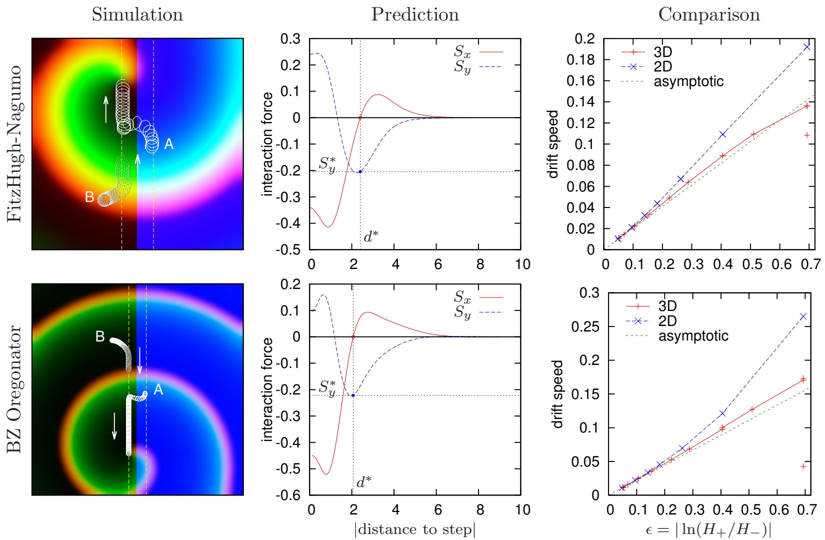


$$F(\vec{R}) = S(d), \qquad d \equiv X - x_s,$$

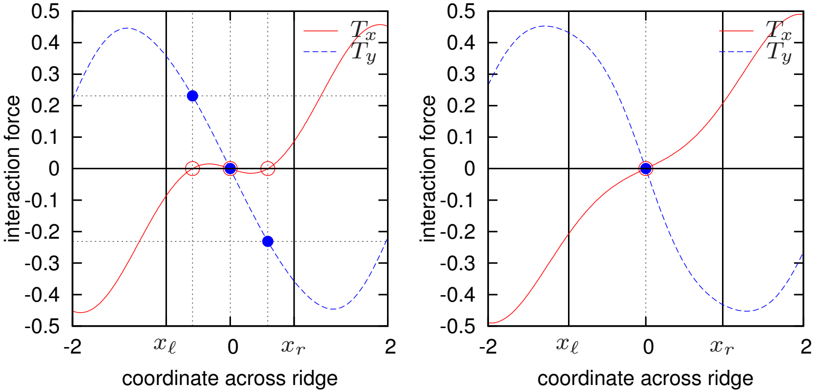
$$S(-d) = S(d) = S_x(d) + \mathrm{i}S_y(d)$$

$$\boxed{\frac{\mathrm{d}X}{\mathrm{d}t} = \epsilon S_x(X), \quad \frac{\mathrm{d}Y}{\mathrm{d}t} = \epsilon S_y(X), \quad \epsilon = \ln\left(\frac{H_+}{H_-}\right)}$$

Attachment and drift near a step: asymptotic vs DNS



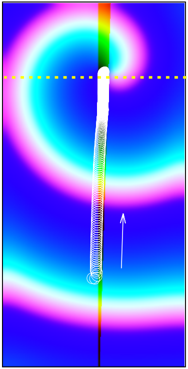
Interaction with a ridge or ditch (FHN)

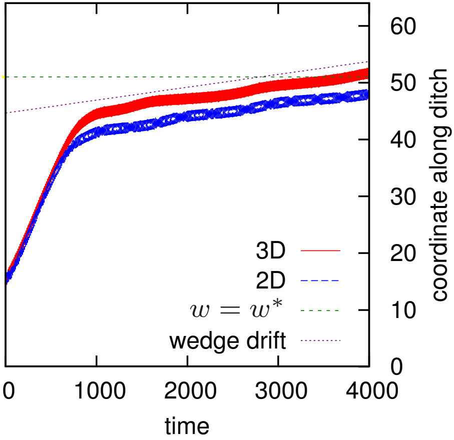


- Two steps of opposite sign, next to each other. Use the superposition principle: $T = T_x + \mathrm{i}\,T_y = S\left(d + \frac{w}{2}\right) - S\left(d - \frac{w}{2}\right)$
- Bifurcation: at some ditch widths, there is "catching" solution, for some only "frozen" solution.

Cuneiform ditch (FHN)

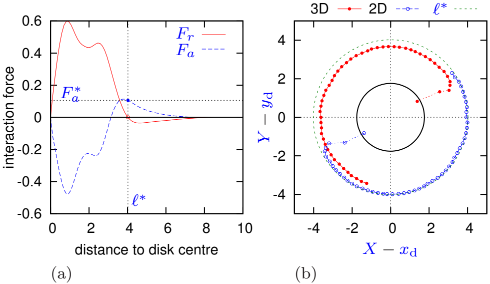
- Ditch with the width varying across the bifurcation value.





- Instead of "frozen" solution, slow drift due to the wedging effect: forces from opposite walls do not fully compensate each other.

Interaction with a circular bump/depression (BZO)



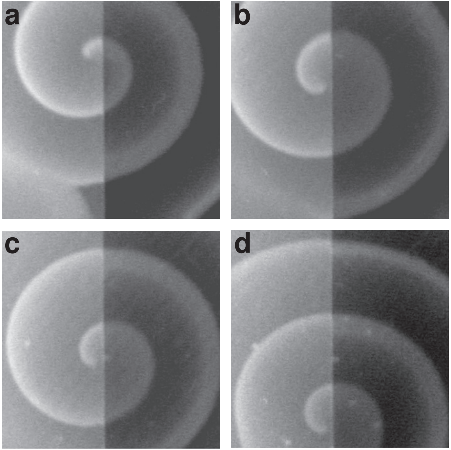
(a) (b)

- Now the interaction force field is axially symmetric: radial component and azimuthal component.
- Zero of radial component gives orbiting radius; corresponging angular component gives orbiting speed.
- These depend on the feature size.

BZ experiment: scroll drift along a step

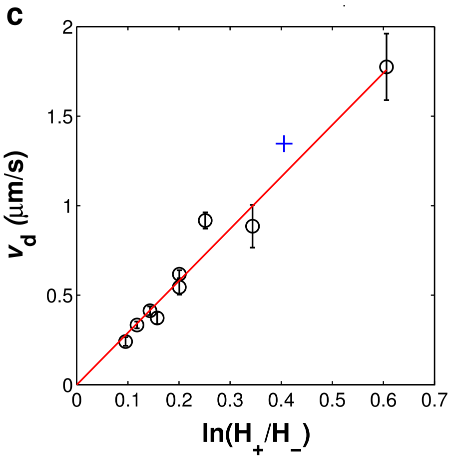
FIG. 1. Four snapshots of a scroll wave in a three-dimensional layer of BZ solution. The system is thin in the left and thick in the right half. The corresponding step induces drift of the scroll wave center. Time between frames: (a) and (b) $50\,\mathrm{min}$, (b) and (c) $50\,\mathrm{min}$, and (c) and (d) $150\,\mathrm{min}$. Field of view: $1.8\,\mathrm{cm} \times 1.8\,\mathrm{cm}$.

H. Ke, Z. Zhang and O. Steinbock "Scroll wave drift along steps, troughs, and corners", *Chaos*, **25**: 064303, 2015



BZ experiment: speed of scroll drift along a step

FIG. 3. Drift velocities v_d as a function of the thick (H_+) and the thin layer height ($H_-(a)$). ...(c) All drift velocities (circles) are jointly graphed against a logarithmic abscissa. The blue cross is obtained from scroll waves drifting along a rectangular trough (see Fig. 4 for details). The red lines are based on the best fit of the proportional dependence $v_d \propto \ln(H_+/H_-)$ to the entire data set.

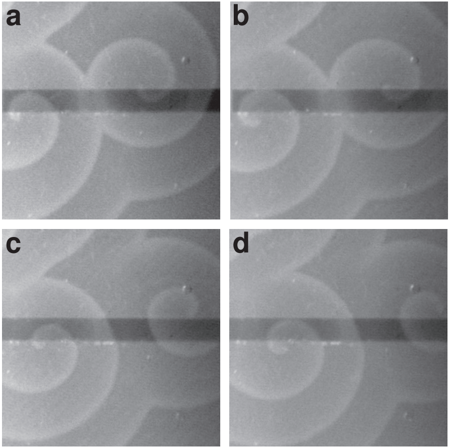


H. Ke, Z. Zhang and O. Steinbock "Scroll wave drift along steps, troughs, and corners", *Chaos*, **25**: 064303, 2015

BZ experiment: scroll drift along a ditch

FIG. 4. Four snapshots of scroll waves drifting along the edges of a rectangular trough. Time between consecutive frames: 27 min. Field of view: 2.2 cm $\times$ 2.2 cm.

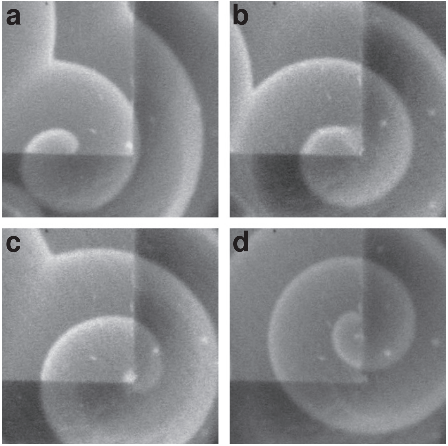
H. Ke, Z. Zhang and O. Steinbock "Scroll wave drift along steps, troughs, and corners", *Chaos*, **25**: 064303, 2015



BZ experiment: scroll drift around a square edge

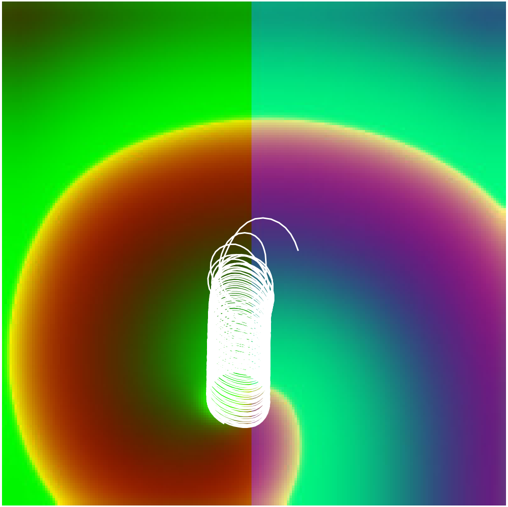
FIG. 5. Four snapshots of a scroll wave drifting along the edge and around the corner of a rectangular plateau. The system is thin in the upper left region. Time between frames: (a) and (b) 60 min, (b) and (c) 8 min, and (c) and (d) 70 min. System heights: $H_+ = 9.0\,\mathrm{mm}$ and $H_- = 5.8\,\mathrm{mm}$. Field of view: $1.8\,\mathrm{cm} \times 1.8\,\mathrm{cm}$.

H. Ke, Z. Zhang and O. Steinbock "Scroll wave drift along steps, troughs, and corners", *Chaos*, **25**: 064303, 2015



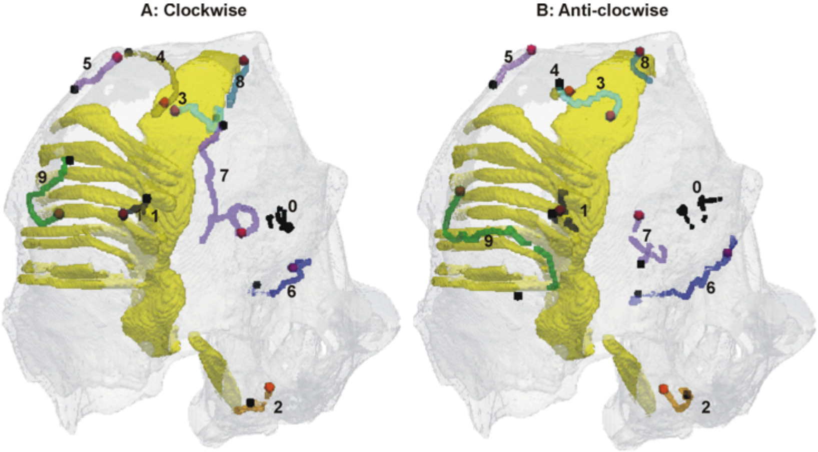
Step-induced drift in modified Courtemanche et al. 1998

- “Non-meandering” modification of a popular model of human atrial tissue.
- This is 2D simulation of a thickness step 1:1.2.



see movies

Drift of spiral/scroll in human atrium geometry



..

S.R. Kharche *et al.* "A Computer Simulation Study of Anatomy Induced Drift of Spiral Waves in the Human Atrium", *BioMed Research International*, 2015: 731386 (2015)

Conclusions

- Geometric features are causing drift, in addition to other well known factors such as parametric inhomogeneities and anisotropy.
- Previously known geometric factors of filament tension and surface curvature do not exhaust all effect.
- Here we have identified an effect related to sharp features. Done it for thin layes.
- Attachment to steps observed in three very different models and in experiment. Response functions are known only numerically, and reason for this "universality" is unclear.
- Similar effects may happen in "full" 3D domains with sharp features on boundaries. Application: anchoring of filaments? Self-wrapping of filaments? Existing 3D drift theory does not (yet) capture this. Challenge for theoreticians!

Acknowledgements

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- Engineering and Physical Sciences Research Council (UK)
- FWO Flanders (Belgium)

GNU lincensed software used

- Response functions: `dxspiral`*
- Direct numerical simulations: `BeatBox`*
- 3D visualization: `ezview`*, based on visualization code of Barkley and Dowle's `EZSCROLL`†

* http://empslocal.ex.ac.uk/people/staff/vnb262/

† http://homepages.warwick.ac.uk/~masax/

THE END

1. Time stepping for (ODE) Markov chain models (T.Stary, V.N. Biktashev, IEEE TBME 62: 1070–1076, 2015)

2. Wave propagation in thin layers (I.V. Biktasheva, H. Dierckx, V.N. Biktashev, PRL 114:068302, 2015)

3. Appendix: details of variable thickness asymptotics

3D $\to$ 2D: coordinate transformation

Original Cartesian coordinates $\vec{r} = (x^j) = (x, y, z)$ vs new curvilinear coordinates $(\rho^j) = (\xi, \eta, \zeta)$, $j = 1, 2, 3$ such that:

- Coordinate ζ is "transmural", that is

$$z(\xi, \eta, 0) = z_{\min}(x(\xi, \eta, 0), y(\xi, \eta, 0)),$$

$$z(\xi, \eta, 1) = z_{\max}(x(\xi, \eta, 1), y(\xi, \eta, 1)).$$

- The other two "intramural" coordinates (ξ, η) are chosen locally orthogonal to ζ, i.e.

$$\frac{\partial \vec{r}}{\partial \xi} \cdot \frac{\partial \vec{r}}{\partial \zeta} = \frac{\partial \vec{r}}{\partial \eta} \cdot \frac{\partial \vec{r}}{\partial \zeta} = 0.$$

- The intramural coordinates match the horizontal Cartesian coordinates in the sense that

$$x(\xi, \eta, 0) = \xi, \qquad y(\xi, \eta, 0) = \eta.$$

3D $\to$ 2D: thermal coordinate

A convenient choice: $\zeta(\vec{r}) = T(\vec{r};\mu)$ which is a solution of the boundary-value problem

$$\begin{aligned}
&\nabla^2 T(x,y,z) = 0, \qquad z \in (0, \mu\tilde{H}(x,y));\\
&T(x,y,0) = 0,\\
&T(x,y,\mu\tilde{H}(x,y)) = 1,
\end{aligned} \tag{13}$$

$\Rightarrow$

$$T = \frac{z}{\mu\tilde{H}} + \frac{\mu^2\tilde{H}^2}{6}\left(1 - \frac{z^2}{\mu^2\tilde{H}^2}\right)\frac{z}{\mu\tilde{H}}\left((\nabla L)^2 - \nabla^2 L\right) + \mathcal{O}\left(\mu^4\right),$$

where

$$\tilde{H} = \tilde{H}(x,y), \qquad L = L(x,y) = \ln\tilde{H}(x,y).$$

3D $\to$ 2D: metric tensor

$$\left[\; g_{jk} \;\right] = \left[\; \frac{\partial \vec{r}}{\partial \rho^j} \cdot \frac{\partial \vec{r}}{\partial \rho^k} \;\right] = \begin{bmatrix} h_{11} & h_{12} & 0 \\ h_{21} & h_{22} & 0 \\ 0 & 0 & g_{33} \end{bmatrix}$$

where

$$\frac{\partial \vec{r}}{\partial \zeta} = \lambda(\zeta) \nabla T(\vec{r}), \qquad T(\vec{r}(\rho^j)) \equiv \zeta, \qquad \vec{r}(0) = (\xi, \eta, 0).$$

The asymptotics for the solution are

$$\lambda = \mu^2 \tilde{H}^2(\xi,\eta) + \mathcal{O}\left(\mu^4\right), \quad \begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} \xi \\ \eta \end{bmatrix} - \frac{1}{2}\mu^2 \tilde{H} \begin{bmatrix} \tilde{H}_x \\ \tilde{H}_y \end{bmatrix} \zeta^2 + \mathcal{O}\left(\mu^4\right),$$

$$z = \mu \tilde{H} \zeta - \frac{1}{6}\mu^3 \tilde{H}^3 \left[(\nabla L)^2 \left(\zeta + 2\zeta^3\right) - \nabla^2 L \left(\zeta - \zeta^3\right) \right] + \mathcal{O}\left(\mu^5\right),$$

$\Rightarrow$

$$h_{ab} = \delta_{ab} + \mathcal{O}\left(\mu^2\right), \qquad a, b = 1, 2,$$

$$g_{33} = \mu^2 \tilde{H}^2 - \frac{1}{3}\mu^4 \tilde{H}^4 \left[(\nabla L)^2 \left(1 + 3\zeta^2\right) - \nabla^2 L \left(1 - 3\zeta^2\right) \right] + \mathcal{O}\left(\mu^6\right).$$

3D $\to$ 2D: Laplace-Beltrami operator

$$\nabla^2 \mathbf{v} = |g|^{-1/2} \frac{\partial}{\partial \rho^j} \left(|g|^{1/2} g^{jk} \frac{\partial \mathbf{v}}{\partial \rho^k} \right)$$

$$= \frac{1}{\mu^2 \tilde{H}^2} \mathbf{v}'' + \nabla L \nabla \mathbf{v} + \nabla^2 \mathbf{v} + G\, \mathbf{v}'' + \mathcal{O}\left(\mu^2\right)$$

where

$$G = G(\xi, \eta, \zeta) = \left(\frac{1}{3} + \zeta^2 \right) (\nabla L)^2 - \left(\frac{1}{3} - \zeta^2 \right) \nabla^2 L,$$

$$' \equiv \partial_\zeta; \qquad \nabla \equiv \nabla_2 = (\partial_\xi, \partial_\eta).$$

3D $\to$ 2D: reaction-diffusion in curvilinear coordinates

$$\partial_t \mathbf{v} = \mathbf{D}\left[\frac{1}{\mu^2\tilde{H}^2}\mathbf{v}'' + \nabla L \nabla \mathbf{v} + \nabla^2 \mathbf{v} + G\,\mathbf{v}'' + \mathcal{O}\left(\mu^2\right)\right] + \mathbf{f}(\mathbf{v})$$

$$\mathbf{D}\partial_3 \mathbf{v}(\xi,\eta,0,t) = \mathbf{D}\partial_3 \mathbf{v}(\xi,\eta,1,t) = 0.$$

Looking for solutions in the form

$$\mathbf{v}(\xi,\eta,\zeta,t;\mu) = \mathbf{u}(\xi,\eta,\zeta,t) + \mu^2\mathbf{g}(\xi,\eta,\zeta,t) + \mathcal{O}\left(\mu^4\right).$$

and consider orders of μ:

$$\mathcal{O}\left(\mu^0\right): \qquad \mathbf{D}\mathbf{u}'' = 0, \quad [\mathbf{D}\mathbf{u}']_{\zeta=0,1} = 0, \quad \Rightarrow \quad \partial_\zeta \mathbf{u} \equiv 0, \quad \mathbf{u} = \mathbf{u}(\xi,\eta,t).$$

$$\mathcal{O}\left(\mu^2\right): \ \mathbf{D}\mathbf{g}'' = \tilde{H}^2\left[\partial_t \mathbf{u} - \frac{1}{\tilde{H}}\mathbf{D}\nabla\left(\tilde{H}\nabla\mathbf{u}\right) - \mathbf{D}\,G\mathbf{u}'' - \mathbf{f}(\mathbf{u})\right], \ [\mathbf{D}\mathbf{g}']_{\zeta=0,1} = 0.$$

3D $\to$ 2D: result

Solvabiliy condition of the $\mathcal{O}\left(\mu^2\right)$ equation as an ODE for $\mathbf{g}$ wrt ζ:

$$\mathbf{D}\mathbf{g}'' = \chi, \quad [\mathbf{D}\mathbf{g}']_{\zeta=0,1} = 0 \qquad \Rightarrow \qquad \chi = 0$$

$$\chi \equiv \partial_t \mathbf{u} - \frac{1}{\tilde{H}} \mathbf{D} \nabla \left(\tilde{H} \nabla \mathbf{u} \right) - \mathbf{f}(\mathbf{u}) = 0$$

The asymptotic expansion is in powers of μ^2, hence

$$\begin{aligned} \partial_t \mathbf{u} &= \frac{1}{\tilde{H}} \mathbf{D} \nabla \left(\tilde{H} \nabla \mathbf{u} \right) + \mathbf{f}(\mathbf{u}) + \mathcal{O}\left(\mu^2\right) \\ &\approx \mathbf{f}(\mathbf{u}) + \mathbf{D} \Delta_2 \mathbf{u} + \mathbf{D} \left(\nabla_2 (\ln H) \cdot \nabla_2 \mathbf{u} \right) \end{aligned}$$

Q.E.D.