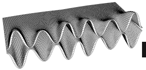
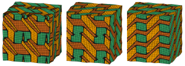
Discovery of Cell Migration Models by Data Driven Variational System Identification and Inverse Reinforcement Learning





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15th World Congress on Computational Mechanics (WCCM-XV)

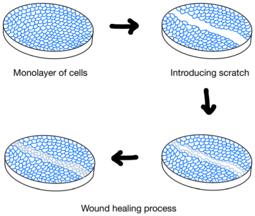
- Individually cells show some heterogeneity in response to external stimuli.
- Normal Heterogeneity in cell behavior drives patterns of cell functionality that create normal tissues.
- Abnormal heterogeneity is a hallmark of diseases like cancer.

MDA-MB-231 breast cancer cells

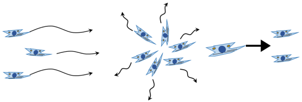
Physical basis for cell dynamics

Cell dynamics obeys the physics of transport problems

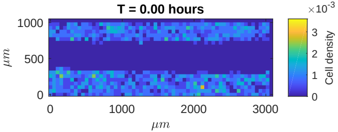
- MDA-MB-231 breast cancer cells; aggressive motility and proliferation
- Scratch assay to study wound healing response



- Partial differential equations to represent the dynamics of cells as a density



$$\frac{\partial c}{\partial t} = \underbrace{-\boldsymbol{v} \cdot \nabla c}_{\text{advection}} + \underbrace{D\nabla^2 c}_{\text{diffusion}} + \underbrace{f}_{\text{reaction}}$$

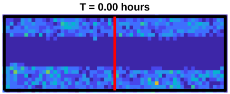


Modeling Cell Migration

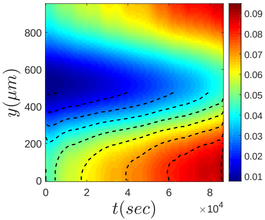
- Physics-based intuition:
  - Cells show both random motion and directed motion
  - Cell density can change due to proliferation and death of cells.
- Hypothesis: The physics of cell migration is determined by a Diffusion-Advection-Reaction system

$$\frac{\partial C}{\partial t} = \underbrace{\nabla\left(D(y,t)\cdot\nabla C\right)}_{\substack{\text{Diffusion}\\\text{(Random motion)}}} - \underbrace{\nabla\cdot\left(\boldsymbol{v}(y,t)C\right)}_{\substack{\text{Advection}\\\text{(Directed motion)}}} + \underbrace{f(y,t)}_{\substack{\text{Reaction}\\\text{(Cell growth/decay)}}}$$

- 1d problem: x-average of cell density data, C; reduce to migration along the y



1. Smooth data using Gaussian filter.
2. x-average: Project on a slice.



Curve fit of contours:

$$\text{form}: y = a\cdot t^b$$

$a \sim 3-10, \qquad b \sim 0.3-0.4$

Dominated by diffusion?

$$\frac{\partial C}{\partial t} = \nabla \left(D(y,t) \cdot \nabla C \right) - \nabla \cdot \left(v(y,t)C \right) + f(y,t)$$

- Diffusion must be positive

$$D = \theta_0 + \theta_1 \widetilde{y}^2 + \theta_2 \widetilde{y}^4$$

where $\theta_0 > 0$ and $\theta_1, \theta_2 \geq 0$

- Advective velocity is zero at the midpoint

$$v = \theta_3 \widetilde{y} + \theta_4 \widetilde{y}^2 + \theta_5 \widetilde{y}^3 + \theta_6 \widetilde{y}^4$$

- Reaction is represented as some polynomial

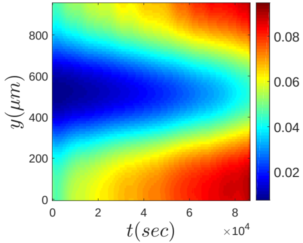
$$f = \theta_7 + \theta_8 \widetilde{y} + \theta_9 \widetilde{y}^2 + \theta_{10} \widetilde{y}^3 + \theta_{11} \widetilde{y}^4$$

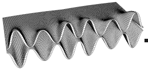
Here $\widetilde{y}$ is non-dimensionalized:

$$\widetilde{y} = \frac{y - 0.5\ell}{\ell}$$

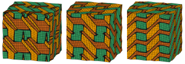
where ℓ is the length of the domain.

- All parameters are time dependent, $\theta_i \equiv \theta_i(t)$.





Parsimonious model selection via VSI



- VSI (Variational System Identification) allows estimation of PDE parameters using the weak form of PDE, naturally treating the Boundary conditions and requiring minimal smoothness constraints on data.
- Weak form:

$$\int_\Omega \frac{\partial C}{\partial t} w d\Omega - \boldsymbol{\chi} \cdot \boldsymbol{\theta} = 0$$

where $\boldsymbol{\chi} = \Bigg[\underbrace{\cdots, -\int \widetilde{y}^n \nabla C \cdot \nabla w d\Omega, \cdots,}_{\text{Diffusion}} \underbrace{\cdots, \int \widetilde{y}^n C \boldsymbol{v} \cdot \nabla w d\Omega, \cdots,}_{\text{Advection}} \underbrace{\cdots, \int \widetilde{y}^n w d\Omega, \cdots}_{\textit{Reaction}} \Bigg]$

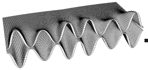
- Finite element discretization and assembly of Residual vector, $\boldsymbol{R}$:

$$\boldsymbol{R} = \mathbf{A}_e \left(\int_{\Omega_e} \frac{\partial C^d}{\partial t} N d\Omega_e - \left[\cdots, -\int \widetilde{y}^n \nabla C^d \cdot \nabla N d\Omega_e, \cdots, \int \widetilde{y}^n C^d \boldsymbol{v} \cdot \nabla N d\Omega_e, \cdots, \int \widetilde{y}^n N d\Omega_e, \cdots \right] \cdot \boldsymbol{\theta} \right)$$

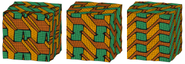
- The coefficients can be found by solving the following optimization problem:

$$\boldsymbol{\theta} = \arg\min_{\widetilde{\boldsymbol{\theta}}} \left(||\boldsymbol{R}(\widetilde{\boldsymbol{\theta}})||_2^2 + \frac{1}{2}\lambda ||\widetilde{\boldsymbol{\theta}}||_2^2 \right)$$

- Parsimony promoting approaches: Regularization, Stepwise regression, Genetic Algorithm



Model refinement using PDE Constrained Optimization



- PDE constrained Optimization estimate parameters that minimizes the difference between the data and forward solution of the PDE.
- Optimization Cost

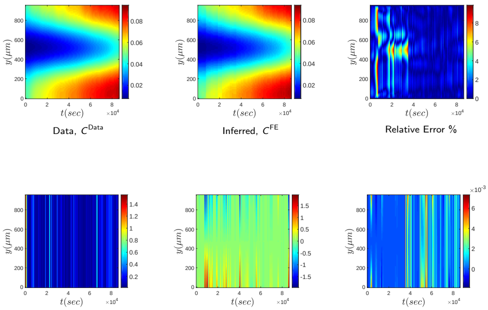
$$\mathrm{Cost}(t|\boldsymbol{\theta}) = \int_0^{\ell} |C^{\mathrm{FE}}(y,t|\boldsymbol{\theta}) - C^{\mathrm{Data}}(y,t)|^2 + |\nabla C^{\mathrm{FE}}(y,t|\boldsymbol{\theta}) - \nabla C^{\mathrm{Data}}(y,t)|^2 dy$$

- The coefficients are found by solving the following optimization problem:

$$\boldsymbol{\theta}(t) = \arg\min_{\widetilde{\boldsymbol{\theta}}} \left(\mathrm{Cost}(t|\widetilde{\boldsymbol{\theta}}) + \frac{1}{2}\lambda||\widetilde{\boldsymbol{\theta}}||_2^2 \right)$$

- Adjoint based optimization is used for estimating gradients
- SUPG Stabilization is used.

- Infer that diffusion (random cell motion) dominates wound healing in this scratch assay
- Bursts of advection and proliferation
- Peclet number and Damkohler number are $<< 1$
- Spatial and temporal variations

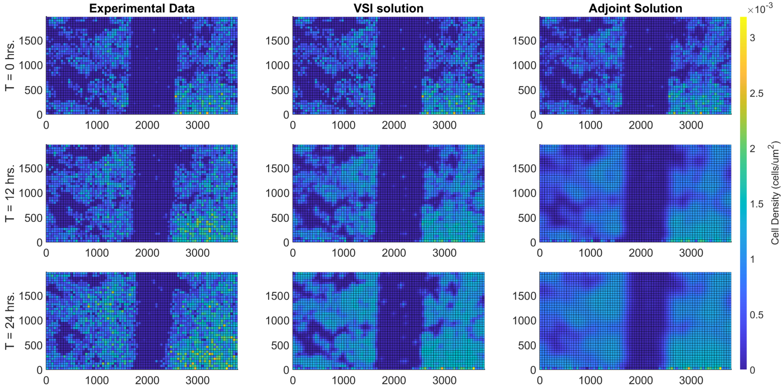


Data, C^{Data} — Inferred, C^{FE} — Relative Error %

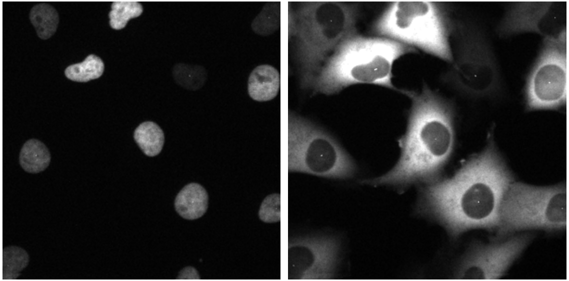
Diffusion, $D(\mu m^2 s^{-1})$ — Advection, $P_e = \frac{vh}{D}$ — Reaction, $\overline{f} = \frac{fh^2}{D}$

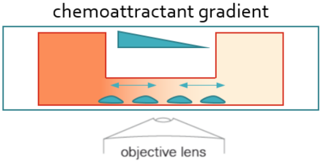
* Normalization length-scale is determined by finite-element size, $h = 12.5\mu m$

- Optimizing drugs for retarding/accelerating wound closure behaviour.

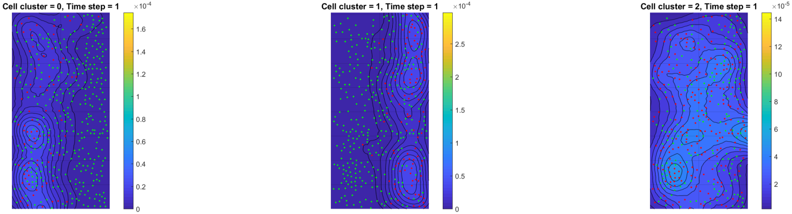


- MDA-MB-231: Aggressively motile breast cancer cell line: Luker lab
- Rosenthal, Iyer, Escudero, Bao, Wu, Ventura, Kleer, Arruda, **KG**, Merajver "$p38\gamma$ Promotes breast cancer cell motility and metastasis through regulation of RhoC GTPase, cytoskeletal architecture, and a novel leading edge behavior", *Cancer Research*, **71**, 6338-6349, 2011
- MDA-MB-231 cancer cells subject to gradient of chemoattractant CXCL12
- Over 24 hours of data
- Heterogeneity of cell response is a significant element of progression in cancer: Spinosa et al. *Cell Mol Bioeng* **1**:49-64, 2021





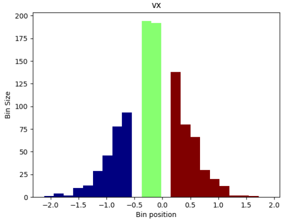
Heterogeneity of cell dynamics does not support a single mean field model



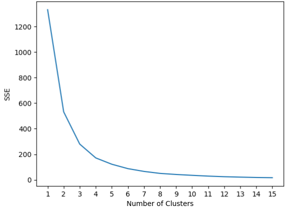
- Cells behave more like individual agents
- Go beyond inference of mean field response: step toward “explaining” cell behavior

Seek distinct sub-populations displaying more homogeneous properties

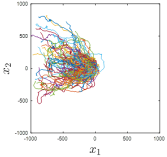
- *k*-means clustering
- Cluster by velocity along CXCL12 gradient
  - Considered diffusivity, persistence, displacement angle, velocity perpendicular to CXCL12 gradient
- Chose $k = 3$ clusters
  - Along, opposed and weakly responsive to CXCL12 gradient



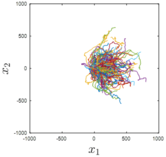
3 clusters



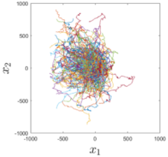
Loss



Cluster 0



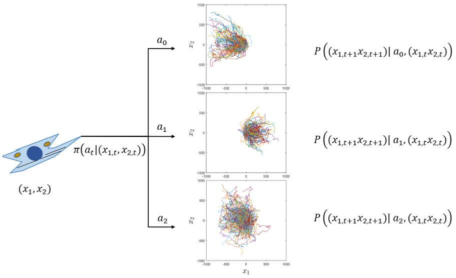
Cluster 1



Cluster 2

Inverse Reinforcement Learning *informed by inferred mean-field physics*:

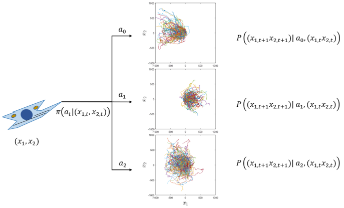
- A cell is in known states $\boldsymbol{x}_t$, for $t \in \{0, \dots, T\}$
- Cell takes an action: $a_t \in \{a_i\}$, to behave as cluster i, for $i \in \{0, \dots n_{\mathrm{cls}-1}\}$
- IRL requires transition probabilities $P(\boldsymbol{x}_{t+1} | a_t, \boldsymbol{x}_t)$ that follows from mean-field physics of cells.
- IRL evaluates:
  - Optimal Policy: $\pi(a_t | \boldsymbol{x}_t)$
  - Instantaneous reward $R(a, \boldsymbol{x})$ for cells
- Maximize total reward collected over all times while concurrently maximizing uncertainty of prediction: *causal entropy* (Ziebart et al., *ICML*, 2010)



VSI of Fokker-Planck equation as mean-field physics of clusters

Max causal entropy algorithm for Inverse Reinforcement Learning needs

- Transition probability function: $P(\boldsymbol{x}_{t+1}|a_t, \boldsymbol{x}_t)$
- A model for the reward: $R(a, \boldsymbol{x}) = \boldsymbol{\theta} \cdot \boldsymbol{\psi}(a, \boldsymbol{x})$



$$\frac{\partial c}{\partial t} = -\nabla \cdot (\nabla \psi(\boldsymbol{x}) c - D \nabla c)$$

- Jordan, Kinderleherer & Otto: *Physica D*, **107**:265-71, 1997; *SIAM J Math Anal*, **29**:1-17, 1998
- Gradient flow of entropy-regularized energy
  - Minimize:

$$\int_{\mathbb{R}^n} \left(\underbrace{\psi(\boldsymbol{x})}_{\text{CXCL12 potential}} \cdot c + \underbrace{Dc \log c}_{\text{entropy}} \right) \mathrm{d}\boldsymbol{x}$$

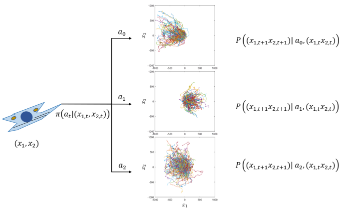
  - *Maximize*:

$$-\int_{\mathbb{R}^n} (\psi(\boldsymbol{x}) c + Dc \log c)\, \mathrm{d}\boldsymbol{x}$$

- Max causal entropy inverse reinforcement learning while maximizing reward; use $\psi_i(\boldsymbol{x})$ as bases in reward: $R(a, \boldsymbol{x})$
- Stationary soln of Fokker Planck: $\exp[-\psi(\boldsymbol{x}/D)] / \int \exp[-\psi(\boldsymbol{x}/D)] \mathrm{d}V$ is the form of policy in max causal entropy inverse reinforcement learning

Max causal entropy algorithm for Inverse Reinforcement Learning needs

- Transition probability function: $P(\boldsymbol{x}_{t+1}|a_t, \boldsymbol{x}_t)$
- A model for the reward: $R(a, \boldsymbol{x}) = \boldsymbol{\theta} \cdot \boldsymbol{\psi}(a, \boldsymbol{x})$



Inferred Fokker-Planck form

Cluster ID (a_i)	$D\ \mu\text{m}^2 s^{-1}$	$\psi_i(\boldsymbol{x})\ \mu\text{m}^2 s^{-1}$	Loss
$a_i = 0$	0.120	$-0.011x_1 + 0.008x_2$	1.8×10^{-15}
$a_i = 1$	0.142	$0.005x_1 + 0.001x_2$	1.8×10^{-15}
$a_i = 2$	0.179	$-0.003x_1 + 0.001x_2$	3.2×10^{-15}

Trans prob fn $P(\boldsymbol{x}_{t+1}|a_t, \boldsymbol{x}_t)$

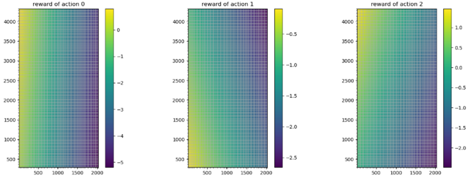
$$\frac{1}{(2\pi)^{d/2}(2D\Delta t)^{d/2}} \exp\left(-\frac{(\Delta x_1 - \psi_{x_1}\Delta t)^2 + (\Delta x_2 - \psi_{x_2}\Delta t)^2}{4D\Delta t}\right)$$

Reward fn $R(a, \boldsymbol{x})$

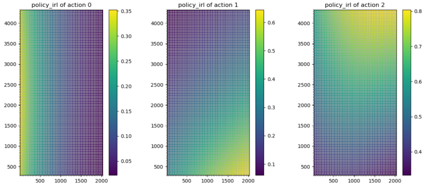
$$\theta_0 \chi_{a=a_0} \psi_0(\boldsymbol{x}) + \theta_1 \chi_{a=a_1} \psi_1(\boldsymbol{x}) + \theta_2 \chi_{a=a_2} \psi_2(\boldsymbol{x})$$

Reward from each action:

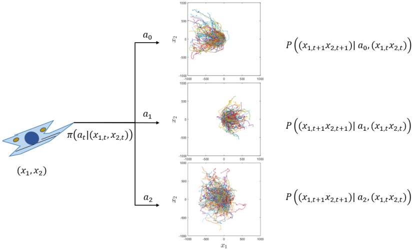
$0.002\psi_0(\boldsymbol{x})$ $-0.0015\psi_1(\boldsymbol{x})$ $0.0039\psi_2(\boldsymbol{x})$

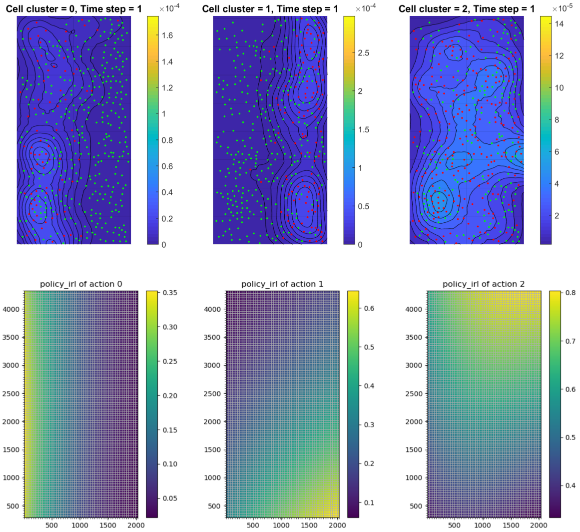


Policies:



- Focus on Action 1 (move against imposed CXCL12 gradient)
- Inverse Reinforcement Learning detects that Cluster 1 moves *away* from its reward
- Even though the inferred basis function, $\psi_1(\boldsymbol{x}) = 0.005x_1 + 0.001x_2$
- "Contrarian" cells




Cell cluster = 0, Time step = 1
$\times 10^{-4}$
Cell cluster = 1, Time step = 1
$\times 10^{-4}$
Cell cluster = 2, Time step = 1
$\times 10^{-5}$
policy_irl of action 0
policy_irl of action 1
policy_irl of action 2

Conclusion

- Variational System Identification gives *mean field* equations; breaks down for sparse data
- Interested in heterogeneity of cell response
- Probabilistic framework of Inverse Reinforcement Learning
- Understand heterogeneous cell behavior in terms of rewards and policy of cells as agents
- Inferred mean field Fokker Planck $\mapsto$ physics-based actions, reward model and transition probability functions
- Theoretical foundation for reward: Fokker-Planck minimizes energy; Max Causal Entropy maximizes -ve energy
- Other actions:
  - Modes of "continuous/discontinuous" migration, polarization/rounding
  - Expression of kinases: ERK, Akt, "intent" to migrate
- Other physics:
  - Forces between cells
  - Contact inhibition and clustering