Neural Network Pipeline for Systems Biology: Solving the Notch Signaling Pathway

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2. Draws tools from both machine learning and scientific computing.
3. Foundations: Domain-aware, avoids over-training, robust.
4. Examples: *Physics-Informed Neural Networks (PINNs)*, Neural Ordinary Differential Equations (ODEs), CNNs for imaging, GNNs for detectors.

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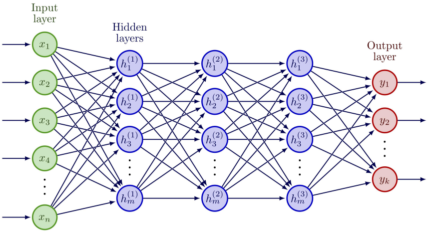
3. Different layers perform different input transformations.
4. Signals travel from the input layer to the output layer through the hidden layers.

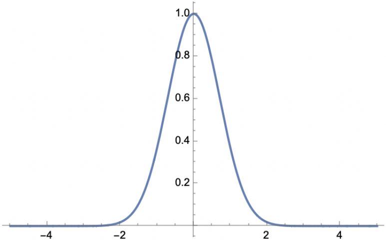


Applications of Neural Networks

1. Pattern recognition (radar systems, face identification, 3D reconstruction)
2. Function approximation (regression analysis, time series prediction)
3. Data and information visualization
4. Spam email filtering
5. Generative AI (including ChatGPT)

A Simple ODE

1. Solve for y as a function of x.
2. The equation is $\dot{y} = -2xy$.
3. The initial condition is $y(0) = 1$.
4. The analytic solution is $y(x) = e^{-x^2}$.

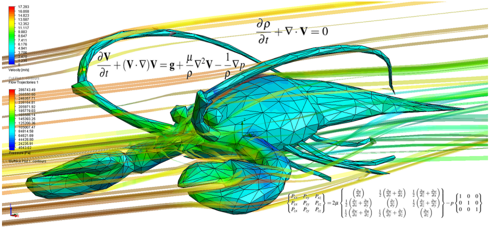


Navier-Stokes Equations

1. PDEs that describe the motion of viscous fluid substances.
2. Solution is a vector field in the form of flow viscosity.
3. Cauchy's momentum equation (convective form):

$$\rho \frac{\mathrm{Du}}{\mathrm{D}t} = -\nabla p + \nabla \cdot \tau + \rho \mathrm{a}$$

4. Navier-Stokes existence and smoothness is one of the Millennium Prize Problems.



Importance and Necessity of NNs

On October 8, Geoffrey Hinton and John Hopfield were awarded the Nobel Prize in Physics "for foundational discoveries and inventions that enable machine learning with artificial neural networks."

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2. Curse of Dimensionality: Many variable problems are *very* computationally expensive.
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4. Hybrid Models: Can combine both physics of the system as well as big data.

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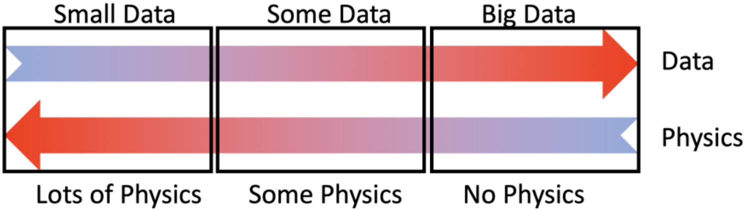
Data Driven Physics Discovery



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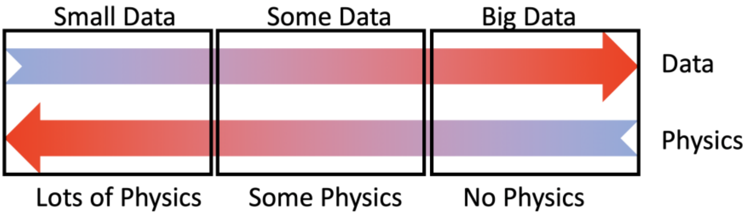

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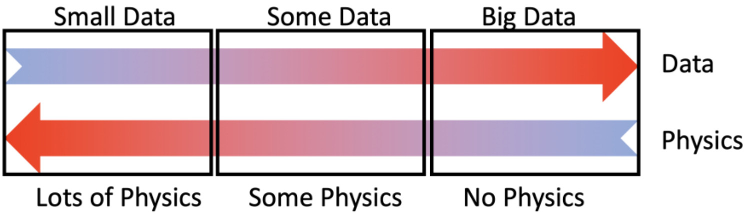

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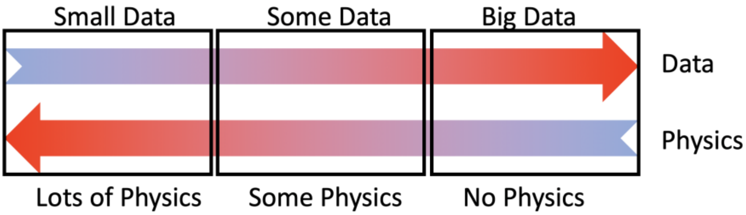

1. Lots of Physics: Finite element methods.
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3. No Physics: Operator and physics learning.[2]

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Inverse Physics-Informed Neural Networks Problem Setup

PINNs are powerful when there is **scarce data** and **not well-known** physics: Inverse Problems.

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Goal: Discover the parameters of a system and make surrogate model.

Inverse Physics-Informed Neural Networks Problem Setup

Consider a PDE system with solution $\mathbf{u}$ over $\Omega \subset \mathbb{R}^d$:

$$\begin{aligned} \mathcal{F}[\mathbf{u}(\mathbf{x}); \gamma(\mathbf{x})] &= 0, & \mathbf{x} \in \Omega \\ \mathcal{B}[\mathbf{u}(\mathbf{x})] &= 0, & \mathbf{x} \in \partial\Omega \end{aligned}$$

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Goal:

$$\boldsymbol{\theta}_u^*, \boldsymbol{\theta}_\gamma^* = \arg \min_{\boldsymbol{\theta}_u, \boldsymbol{\theta}_\gamma} \mathcal{L}(\boldsymbol{\theta}_u, \boldsymbol{\theta}_\gamma)$$

for loss function $\mathcal{L}$.

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$$\mathcal{L}_s(\theta) = \frac{1}{N_s} \sum_{i=1}^{N_s} (\hat{u}(\mathbf{x}_r^i) - u(\mathbf{x}_r^i))^2$$

$$\mathcal{L}_r(\theta, \lambda_r) = \frac{1}{N_r} \sum_{i=1}^{N_r} (\mathcal{F}[\hat{u}, \hat{\gamma}](\mathbf{x}_r^i))^2$$

$$\mathcal{L}_b(\theta, \lambda_b) = \frac{1}{N_b} \sum_{i=1}^{N_b} (\mathcal{B}[\hat{u}](\mathbf{x}_b^i))^2$$

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4. Total loss: $\mathcal{L}(\theta) = \mathcal{L}_s(\theta) + \lambda_r\mathcal{L}_r(\theta) + \lambda_b\mathcal{L}_b(\theta)$

Alphabet of PINNs

- Hard and Soft Constrained PINNs
- VPINN: Variational PINNs (and hp-VPINN: h, p refined variational PINNs)
- GPINN: Gradient-enhanced PINN
- CPINN: Conservative PINNs
- XPINN: Extended PINNs
- fPINN: PINNs for fractional PDEs
- sPINN: PINNs for stochastic DEs
- PI-GAN: Physics-informed Generative Adversarial Network

Applications of PINNs

1. Physics: Heat transfer, structural mechanics, electromagnetism, and fluid dynamics.[3]

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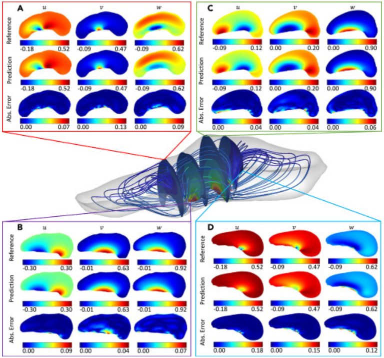

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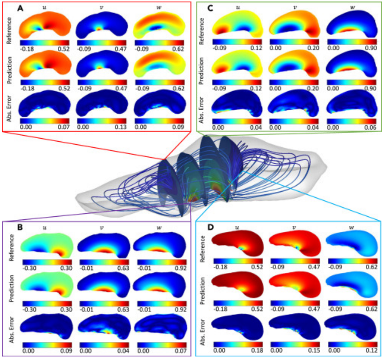

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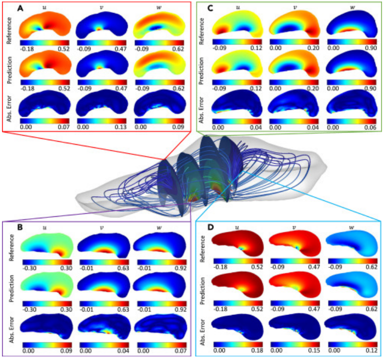

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Application of PINNs in Systems Biology

In Systems-Biology related problems, instead of dealing with *one* PDE, we instead have to deal with a system of coupled ODEs (though this can be extended to PDEs). Just like PINNs, we have the problems of scarce data and fuzzy measurements.

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Solution: Utilise... systems Biology-informed NNs! Or, sBINNs for short.

$$\mathcal{L}(\theta) = \mathcal{L}_S(\theta) + \sum_{\mathcal{F} \in \text{ODE Residuals}} \mathcal{L}_{\mathcal{F}}(\theta)$$

sBINNs specific problem

The system of ODEs that we focused on was specifically the Notch signalling pathway mentioned at the beginning. For the sake of clarity, the ODEs will be shown here. There are 22 state variables:

$$
\begin{aligned}
\frac{d[\mathrm{Dl4}_{\mathbf{c1}}]}{dt} &= -\left(k_f \cdot \mathrm{Dl4}_{c\mathbf{1}} \cdot \mathrm{Notch1}_{c\mathbf{2}} + k_r \cdot \mathrm{Dll1\_Notch1}_{c\mathbf{2}}\right) \\
&\quad -\left(k_f \cdot \mathrm{Dl4}_{c\mathbf{1}} \cdot \mathrm{Notch1}_{c\mathbf{1}} + k_r \cdot \mathrm{Dll4\_Notch1}_{c\mathbf{1}}\right) \\
\frac{d[\mathrm{Notch1}_{c\mathbf{1}}]}{dt} &= -\left(k_f \cdot \mathrm{Dl4}_{c\mathbf{2}} \cdot \mathrm{Notch1}_{c\mathbf{1}} + k_r \cdot \mathrm{Dll4\_Notch1}_{c\mathbf{1}}\right) \\
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\frac{d[\mathrm{Dl4\_Notch1}_{c\mathbf{1}}]}{dt} &= \frac{G_s \cdot k_{\mathbf{cat}} \cdot \mathrm{Dl4}_{c\mathbf{1}} \cdot \mathrm{Notch1}_{c\mathbf{1}}}{K_m + \mathrm{Dl4\_Notch1}_{c\mathbf{1}}} - \frac{\mathrm{tetAhe} \cdot \mathrm{Hes1}_{c\mathbf{1}c\mathbf{2}}}{K_p + \mathrm{NICD}_{c\mathbf{1}c\mathbf{2}}} \\
\frac{d[\mathrm{NICD}_{c\mathbf{1}}]}{dt} &= -\frac{\mathrm{tetAhe} \cdot \mathrm{Hes1}_{c\mathbf{1}c\mathbf{2}}}{K_p + \mathrm{NICD}_{c\mathbf{1}c\mathbf{2}}} \\
\frac{d[\mathrm{Jagged1}_{c\mathbf{1}}]}{dt} &= -k_{\mathbf{deg\_Jag}} \cdot \mathrm{Jagged1}_{c\mathbf{1}} - \left(k_{\mathbf{on\_cis}} \cdot \mathrm{Jagged1}_{c\mathbf{1}} \cdot \mathrm{Notch1}_{c\mathbf{1}} + k_{\mathbf{on\_cis}} \cdot \mathrm{JagNotch}_{c\mathbf{1}}\right) \\
\frac{d[\mathrm{Jag\_Notch}_{c\mathbf{1}}]}{dt} &= k_{\mathbf{on\_cis}} \cdot \mathrm{Jagged1}_{c\mathbf{1}} \cdot \mathrm{Notch1}_{c\mathbf{1}} + k_{\mathbf{on\_cis}} \cdot \mathrm{JagNotch}_{c\mathbf{1}} \\
\frac{d[\mathrm{Notch\_jag2}_{c\mathbf{1}}]}{dt} &= k_f \cdot \mathrm{JagNotch\_jagc1}_{c\mathbf{1}} \cdot \mathrm{Notch1}_{c\mathbf{2}} + k_r \cdot \mathrm{JagNotch\_jagc1}_{c\mathbf{1}} - \left(k_f \cdot \mathrm{Dl1}_{c\mathbf{2}} \cdot \mathrm{Notch1}_{c\mathbf{1}} + \right. \\
d[\mathrm{pR2}_{c\mathbf{1}}]
\end{aligned}
$$

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Parameter	kf_{dllN}	kp_{R2}	kdp_{R2}	kr_{dllN}	Km	kcat	$kdeg_{\mathrm{NICD}}$	$kdeg_{\mathrm{Notch}}$	$kdeg_{\mathrm{Dll4}}$	kp_{Dll}	teta	$kdeg_{\mathrm{Hes1}}$	Kp_{Hes}
Identifiability	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓
Parameter	tetaHe	kon_{cis}	$kdeg_{\mathrm{Jag}}$	kr_{jagNotch}	kr_{cis}	kf_{jagNotch}	Kp_{Jag}	tetaJag	$kdeg_{\mathrm{pR2}}$	$kdeg_{\mathrm{iR2}}$	Gs	$kform_{\mathrm{Notch}}$	kp
Identifiability	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	×

Table 1: Structural Identifiability of Notch model with STRIKE-GOLDD and StucturalIdentifiability.jl.

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Identifiability	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓
Parameter	tetaHe	kon_{cis}	$kdeg_{Jag}$	$kr_{jagNotch}$	kr_{cis}	$kf_{jagNotch}$	Kp_{Jag}	tetaJag	$kdeg_{pR2}$	$kdeg_{iR2}$	Gs	$kform_{Notch}$	kp
Identifiability	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	×

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Ultimately, we focused on $k_{f,\mathrm{DllN}}$, $k_{p,\mathrm{R2}}$, $k_{\mathrm{deg,NICD}}$, $k_{\mathrm{deg,Notch}}$, $k_{\mathrm{deg,Dll4}}$, θ, and $k_{\mathrm{deg,pR2}}$, with $k_{\mathrm{deg,NICD}}$ being the most sensitive.

Sensitivity Analysis

After selecting those 8 parameters, we run a standard OAT (one-at-a-time) sensitivity analysis to determine *how fast* each parameter should get trained in our inverse-SBINN setup.

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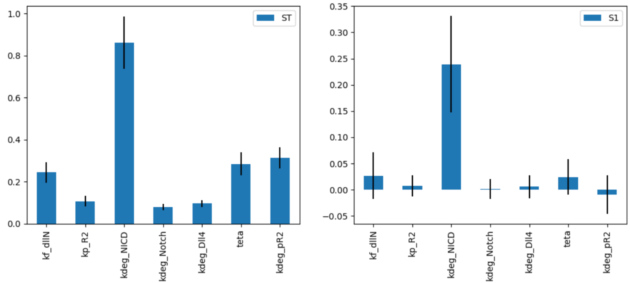

Figure 1: Sensitivity Analysis for the Notch ODE problem on parameters of interest.

Model Results

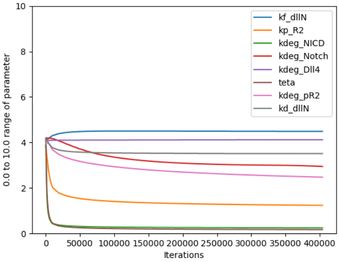

Figure 2: Parameters we tracked during the training of the final SBINN model.

Name	Value
kf_dllN	0.103
kp_R2	0.979
kdeg_NICD	1.84
kdeg_Notch	0.437
kdeg_Dll4	0.178
teta	2.03
kdeg_pR2	0.556
kd_dllN	0.307

Figure 3: Relative values attained after training.

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- Parents, family, and friends for supporting us throughout our endeavors.
  - Without them, where would we be? (Not in Boston).

Thank You

Agniv Sarkar, Kartik Ramachandrula, Alex Huang

1. Introduction
2. PINNs
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4. Conclusion
5. References

[1] K. Hornik, M. Stinchcombe, and H. White, "Multilayer feedforward networks are universal approximators," *Neural Networks*, vol. 2, no. 5, pp. 359–366, 1989.

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