

Module 2: Morphogen gradients

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Aim:

- Adapt an established theoretical model to a fundamental developmental patterning process.
- Thereby going through the typical modeling workflow seen in Module 1.

Description:

- Read abstract of Yu et al.
- Derive diffusion equation from 1st and 2nd Fick's law
- Morphogen interpretation entails morphogen binding thereby eliminating it from (observed) diffusible pool → derive Eq. (1)
- Run Gradient.xml to see gradient building up
- Solve steady state of Eq. (1) analytically, $c(x) = c_0 \exp(-x/\lambda)$ $\lambda = \sqrt{D/k}$
- Find parameter value for D in the paper (Fig.3, why multiple?, relation between molecule weight and D?, fluorescent tag is source of artefacts - let's see how big they are)
- Calculate k from λ given in the text above Fig.4 (which D corresponds to the data?)
- Discuss role of Dynamin and Rab5 for ligand-receptor uptake
- Using Morpheus, reproduce the results of Fig.4B and document in protocol, verify role of Dynamin and Rab5
- Discuss role of right boundary condition, vary system size to explore changing steady state conc. at same position for no flux bc. in small vs. large system size
- Estimate D for naked Fgf8
- Simulate true morphogen profile and discuss difference to measured profile, just control case → this is a 50% tagging artefact
- Study Wolpert's French Flag model, Discuss idea qualitatively
- Change gradient decay length and observe positions of tissue boundaries
- Change threshold values and observe positions of tissue boundaries
- Change cell size (node length) and observe positions of tissue boundaries
- Extend the morphogen PDE-model by a cell differentiation model = bistable reporter gene that controls differential gene expression downstream and is activated by the morphogen (Hill+additive morphogen-degradation), Which diffusion constant should the gene equation get? ($D=0$)
- Compare your model extension to Gradient_Interpreter.xml
- Simulate for different morphogen degradation rate and diffusion constant, observe position of emergent differentiation boundary

Paper:

- Wolpert L (1969). "Positional information and the spatial pattern of cellular differentiation". *J. Theor. Biol.* 25 (1): 1-47. doi:10.1016/S0022-5193(69)80016-0. PMID 4390734. [link](#)
- Yu S R et al. (2009). "Fgf8 morphogen gradient forms by a source-sink mechanism with freely diffusing molecules" *Nature* 461, 533-536. doi:10.1038/nature08391. [link](#)

Morpheus models:

[French Flag: Morphogen gradient](#)

h Gradient.xml |h

```
<MorpheusModel version="1">
  <Description>
    <Title>Example-MorphogenGradient</Title>
  </Description>
  <Space>
    <Lattice class="linear">
      <Size value="100 0 0"/>
      <BoundaryConditions>
        <Condition boundary="x" type="noflux"/>
        <Condition boundary="-x" type="constant"/>
      </BoundaryConditions>
      <NodeLength unit="micron" value="1"/>
    </Lattice>
  </Space>
  <Time>
    <StartTime value="0"/>
    <StopTime value="500"/>
    <SaveInterval value="0"/>
    <RandomSeed value="1"/>
  </Time>
  <PDE>
    <Layer symbol="A" name="activator">
      <Diffusion rate="1" unit="µm²/s"/>
      <Initial>
        <InitPDEExpression>
          <Expression>rand_uni(0,0.01)</Expression>
        </InitPDEExpression>
      </Initial>
      <BoundaryConditions>
        <Condition boundary="-x" value="1.0"/>
      </BoundaryConditions>
    </Layer>
    <System solver="runge-kutta" time-step="1">
      <DiffEqn symbol-ref="A">
        <Expression>- k * A</Expression>
      </DiffEqn>
      <Constant symbol="k" value="0.01"/>
    </System>
  </PDE>
  <Analysis>
    <SpaceTimeLogger interval="20">
      <Layer symbol-ref="A"/>
      <Plot interval="500" every="0" terminal="png" persist="true"/>
    </SpaceTimeLogger>
    <Logger interval="10">
      <Format string="A"/>
      <Input>
        <PDE mapping="all"/>
      </Input>
    </Logger>
  </Analysis>
</MorpheusModel>
```

```

    </Input>
    <Plot terminal="png" persist="true">
      <X-axis column="2"/>
      <Y-axis columns="5"/>
      <color-bar column="1"/>
    </Plot>
  </Logger>
  <!-- <Disabled>
  <Gnuplotter interval="500">
    <Terminal name="png"/>
    <PDE symbol-ref="A"/>
  </Gnuplotter>
</Disabled>
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  </Analysis>
</MorpheusModel>

```

h Gradient_Interpreter.xml |h

```

<MorpheusModel version="1">
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  </Description>
  <Space>
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        <Condition boundary="-x" type="constant"/>
      </BoundaryConditions>
      <NodeLength unit="micron" value="1"/>
    </Lattice>
  </Space>
  <Time>
    <StartTime value="0"/>
    <StopTime value="500"/>
    <SaveInterval value="0"/>
    <RandomSeed value="1"/>
  </Time>
  <PDE>
    <Layer symbol="A" name="activator">
      <Diffusion rate="1" unit="µm²/s"/>
      <Initial>
        <InitPDEExpression>
          <Expression>rand_uni(0,0.01)</Expression>
        </InitPDEExpression>
      </Initial>
      <BoundaryConditions>
        <Condition boundary="-x" value="1.0"/>
      </BoundaryConditions>
    </Layer>
  </PDE>

```

```
        </BoundaryConditions>
</Layer>
<Layer symbol="G" name="Gene">
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    <Initial>
        <InitPDEExpression>
            <Expression>0</Expression>
        </InitPDEExpression>
    </Initial>
</Layer>
<System solver="runge-kutta" time-step="0.01">
    <DiffEqn symbol-ref="A">
        <Expression>- k * A</Expression>
    </DiffEqn>
    <Constant symbol="k" value="0.01"/>
    <DiffEqn symbol-ref="G" name="threshold activation">
        <Expression>A+G^2/(0.2^2+G^2) - 1*G</Expression>
    </DiffEqn>
</System>
</PDE>
<Analysis>
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        <Layer symbol-ref="A"/>
        <Plot interval="100" every="0" terminal="png" persist="true"/>
    </SpaceTimeLogger>
    <Logger interval="10">
        <Format string="A"/>
        <Input>
            <PDE mapping="all"/>
        </Input>
        <Plot terminal="png" persist="true">
            <X-axis column="2"/>
            <Y-axis columns="5"/>
            <color-bar column="1"/>
        </Plot>
    </Logger>
    <!-- <Disabled>
    <Gnuplotter interval="500">
        <Terminal name="png"/>
        <PDE symbol-ref="A"/>
    </Gnuplotter>
</Disabled>
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    <SpaceTimeLogger interval="5">
        <Layer symbol-ref="G"/>
        <Plot interval="100" every="0" terminal="png" persist="true"/>
    </SpaceTimeLogger>
</Analysis>
</MorpheusModel>
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From:

<https://imc.zih.tu-dresden.de/wiki/morpheus/> - **Morpheus**

Permanent link:

<https://imc.zih.tu-dresden.de/wiki/morpheus/doku.php?id=documentation:course:module2>

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