AngioFE: A Continuous-Discrete Model of Angiogenesis that Couples Neovessel Growth with Matrix Deformation

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Getting Started:

Running a simulation with AngioFE requires five files:

- AngioFE plugin (Win: `AngioFE.dll`, Linux: `libangiofe.so`, OSX: `libangiofe.dylib`)
- FEBio2 executable
- FEBio configuration file (`febio.xml`), pointing to the location of the plug-in file.
- FE model input file for FEBio (`femodel.feb`)
- AngioFE control file (`angiofe.txt`)

The FEBio configuration file is an `.xml` file that is used to specify the location of plug-in files that can be executed at run-time. An example of a configuration file pointing to the location of the AngioFE plug-in using the `import` command can be found below:

```
<?xml version="1.0" encoding="ISO-8859-1"?>
<febio_config version="1.0">
	<import>C:\AngioFE.dll</import>
	<linear_solver type="pardiso"/>
</febio_config>
```

Executing the AngioFE plug-in within FEBio requires special syntax in the command line:

```
C:\febio2.exe –i femodel.feb –cnf febio.xml –task=angio angiofe.txt
```

The `–i` argument for the executable specifies the name of the FE model input file and the `–task` argument tells FEBio to execute the task `angio` within the plug-in file. The input information for the plug-in file is stored in the AngioFE control file which is the final argument.

FEBio Input File:

All the information relating to the FE problem is stored in the FE model input file (`femodel.feb`). This includes control information for the solver, the constitutive model, nodal positions and element connectivity, and output configuration. This input file can be created in the usual manner using the PreView pre-processing software, part of the FEBio software suite.

The parameters controlling the sprout stress fields generated by neovessels during the simulation and the material coefficients are specified in the material section of the input file. The sprout

stresses are represented using a material class in FEBio known as the `angio` material. This material creates the active stresses that drive the deformation and remodeling of the matrix. Each sprout tip is assigned a local directional sprout force according to the following equation,

$$\boldsymbol{\sigma}_s(\boldsymbol{x}) = ae^{-b\|r\|}\cos^N\left(\frac{\psi}{2}\right)\hat{\boldsymbol{r}}\otimes\hat{\boldsymbol{r}},$$

where $\boldsymbol{r}$ is the vector drawn from $\boldsymbol{x}$ to the sprout tip and ψ is the angle formed between $\boldsymbol{r}$ and the direction of the sprout. If using a symmetry model, these sprout stresses are mirrored across symmetry planes

This material is used in a solid mixture with the constitutive model. Any constitutive model can be chosen to represent the vascularized constructs, although changes might be needed in the source code for certain options. An example of the material section of a FEBio file used in a recent study can be found below [1]. This example uses Maxwell fluid-like viscoelasticity to dissipate stress within the gel, as we have found that stresses in collagen gels during angiogenesis are dissipative rather than accumulative [2]. The vascularized construct is represented by a mixture of a microvessel (neo-Hookean) and ECM material (EFD neo-Hookean), and the microvessel volume fraction is used to weigh the individual stress contributions throughout the simulation. See the FEBio theory manual for more information about these specific constitutive models.

Parameter	Description	Value
a	Sprout stress magnitude (per single sprout)	3.72 μPa
b	Sprout stress range	1/250 μm^{-1}
N	Sprout stress width (cosine exponent)	2
E_{vess}	Microvessel constitutive model: Modulus	3.452 kPa
E_M	ECM constitutive model: Stiffness of ground matrix (governs compressive response)	34.52 Pa
E_{fib}	ECM constitutive model: Nonlinear fiber stiffness (governs tensile response)	345.2 Pa
τ	ECM constitutive model: Viscoelastic time constant	1.08 seconds

Comments are given in italic and green, but should not be included when constructing the actual input file. Fundamental units for this problem were μm for distance, kg for mass, and seconds for time.

```
<Material>
      <material id="1" type="solid mixture">
            <density>5e-16</density>
            <solid type="angio">
                  <a>3.72e-12</a>     // Sprout stress: a
                  <b>0.004</b>        // Sprout stress: b
                  <N>2.0</N>          // Sprout stress: N
            </solid>
            <solid type="viscoelastic">
                  <t1>0.00005</t1>    // Constitutive model: τ
```

```
                    <g0>0.0</g0>        // This combination of g0 and g1
                    <g1>1.0</g1>        // specify Maxwell fluid viscoelasticity
                    <elastic type="solid mixture">
                          <solid type="neo-Hookean">
                                <E>0.003452</E>     // Constitutive model: E_vess
                                <v>0.0</v>
                          </solid>
                          <solid type="EFD neo-Hookean">
                                <E>0.00003452</E>   // Constitutive model: E_M
                                <v>0.</v>
                                <beta>2.5,2.5,2.5</beta>
                                <ksi>0.0003452,0.0003452,0.0003452</ksi>     // E_fib
                                <mat_axis type="local"></mat_axis>
                          </solid>
                    </elastic>
              </solid>
        </material>
</Material>
```

AngioFE Control File:

The AngioFE control file is a text file that contains all the input parameters for the growth model (`angiofe.txt`). Lines in this file begin with a prefix character, "`%`" denotes a comment, which is ignored, and the "`>`" denotes a parameter to be read in. Specifying a parameter requires a special parameter identifier string and the value it is to be set at. Any parameter that is not specified will be set to its default value during initialization.

Here is an example of comment lines and input lines in a control file:

```
% AngioFE
% Control file

> brnch_ch 0.1
> matx_cnd 0
> matx_den 3.0
```

Input lines require the exact spelling of parameter identifiers and spacing as seen in this example. A list of parameters that can be specified in the control file can be found below. The '*x*' following the identifier is a placeholder for the desired value of the parameter.

Parameter Identifier	Value Type	Description	Default Value
`> branch` *x*	Integer	Flag to turn branching on (1) or off (0)	1
`> anast` *x*	Integer	Flat to turn anastomosis on (1) or off (0)	1
`> brnch_ch` *x*	Double	Branching probability	0.1
`> matx_cnd` *x*	Integer	Matrix alignment condition: 0 = random fibril network, 1 = fibril network aligned along *x* direction	0
`> matx_den` *x*	Double	Matrix density (mg/ml), used for growth model only to scale growth rate, branching (not used in the FE model, but updated based on the results from FEBio)	3.0
`> comp_mat` *x*	Integer	Flag to use the composite constitutive model:	0

		0 = constant volume fraction 1 = Re-calculate volume fraction after each growth step	
> nfrag *x*	Integer	Number of initial microvessel fragments	3
> max_time *x*	Double	Max time of the simulation (days)	4.0
> dt *x*	Double	Initial step size in the growth model (days)	0.25
> anst_dst *x*	Double	Distance threshold for anastomosis (μm)	25.0
> lngth_adj *x*	Double	Length adjuster, used to scale growth rate depending on different conditions the user might want to simulate	1.0
> gweights *x x*	Double	Values that weigh the individual contributions to microvessel growth. The first value designates the weight of ECM fibril guidance, and the second weight designates the value for the persistence component	10.0, 100.0
> gel_bc *x*	Char	Indicates the collagen fibril boundary conditions: 'u' – Unconstrained, fibrils are parallel to all boundary faces (not at symmetry planes however) 'l' – Long-axis constrained, parallel fibrils at all gel boundary faces except the face representing the constraining mesh (face normal to -*x* direction) 's' – Short-axis constrained, similar to the long-axis constrained but for the face normal to the -*y* direction instead	u
> sub_cyc *x*	Integer	AngioFE allows the growth step to be split into sub-cycle growth steps, and the model solves for the deformation after each sub-growth step	1 (i.e., no sub-growth steps)
> front_bc *x*	Char	Designates the vessel boundary condition for the 'front boundary face, normal to the –*y* direction: 'w' = flat wall BCs, vessels that encounter this type of boundary will stop growing 'i' = in-plane BCs, vessels that encounter this type of boundary will change their growth direction to grow along the boundary face 'b' = bouncy wall BCs, vessels that encounter this type of boundary will 'bounce' off the boundary, reflecting their growth direction with respect to the boundary normal	w
> right_bc *x*	Char	Same as front_bc, but for the 'right' face normal to the +*x* direction	w
> back_bc *x*	Char	Same as front_bc, but for the 'back' face normal to the -*y* direction	w
> left_bc *x*	Char	Same as front_bc, but for the 'left' face normal to the -*x* direction	w
> bottom_bc *x*	Char	Same as front_bc, but for the 'bottom' face normal to the -*z* direction	w
> top_bc *x*	Char	Same as front_bc, but for the 'top' face normal to the +*z* direction	w
> rseed *x*	Integer	Specifies the seed for the random number generator	1234567890
> Sx *x*	Double	If mirroring sprout stresses across symmetry plans, this parameter gives the position along the *x*-axis of the *yz*-symmetry plane (μm)	0.0 (i.e., no symmetry mirroring)
> Sy *x*	Double	Same as Sx, but gives the position along the *y*-axis of the *xz*-symmetry plane	0.0 (i.e., no symmetry mirroring)
> Sz *x*	Double	Same as Sx, but gives the position along the *z*-axis of the *xy*-symmetry plane	0.0 (i.e., no symmetry mirroring)
> stiff_fact *x*	Double	This parameter can be used to scale the amount of nodal displacement that is interpolated to the microvessel positions.	1.0

		A value of 1.0 does not scale nodal displacement, while a value of 0.0 will not assign any nodal displacement to the vessels.	

Output Files:

AngioFE and FEBio generate several output files that can be used to analyze the results of simulations (note that the `.ang` file format used by AngioFE is just a text file format and can be opened similar to a `.txt` file):

- `femodel.xplt` – This file format contains all the data for the FE model and can be opened using the PostView software, part of the FEBio software suite. This file will have the same name as the FE model input file.
- `femodel.log` – Log file for FEBio, this file will have the same name as the FE model input file.
- `angiofe.log` – Log file for AngioFE, this file will have the same name as the AngioFE control file.
- `out_coll_fib.ang` – Collagen fibril orientation for each node at the final time point of the simulation.
- `out_coll_fib_init.ang` – Collagen fibril orientation for each node at the initial configuration.
- `out_data.ang` – Contains all microvessel positions at the final time point of the simulation.
- `out_ecm_den.ang` – Contains the final and initial matrix density for each node.
- `out_time.ang` – Gives the relationship between simulation time in AngioFE and steps within FEBio.
- `out_vess_state.ang` – Contains the position of all microvessels at all time points, this file can be read in by PostView using the 'Add Lines' feature.

Example and Prebuilt Libraries:

A simple example is included in the AngioFE/Example directory and can be run using the syntax in the "Getting Started" section. The febio.xml file in that directory needs to be edited to use the plugin for the appropriate platform. Plugins for several platforms are included in the build/lib directory.

To reproduce the angiofe.png image in that directory, follow these steps:

- Open febiomodel.xplt in PostView.
- On the tools tab, click Add Lines and browse to open out_vess_state.ang in the Example directory, then click Apply.
- On the Material Manager tab, lower the Transparency to about 0.50.
- Run the simulation to the end time step.

References:

[1] Edgar et al., Biomech Model Mechanobiol, In Submission.

[2] Underwood et al., Am J Physiol Heart Circ Phyiol, 2014 Jul 15;307(2):H152-64