Graphically exploring diffusion of brain-penetrating nanoparticles

Effects of timescale and particle chemistry on effective diffusion coefficient and particle trajectories

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Important Neurological Problems

- Neurological disorders account for 13% of the global burden of disease ($700 billion annually)
- Therapeutics for neurological disorders take 35% longer to develop than drugs for other disorders
- Childhood neurodevelopmental disorders are chronic disabilities with no effective cure, and are often underserved by novel drug delivery technologies, which primarily focus on adults.

Blood-brain barrier and therapeutic challenges

Less than 5% of therapeutics are able to cross the blood-brain barrier (BBB). Lack of penetration within the brain parenchyma is the most cited reason for failure of clinical trials. There is great opportunity to bring nanotherapeutic approaches to neurodevelopmental disorders, with results that can then be translated to adult neurological disorders. Nanotechnology-based approaches provide potential platforms for site-specific, controlled release of therapeutics to central nervous system (CNS) diseases, which are both targeted to the regions of the brain that contain diseased cells, as well as to specific cell types within those regions. Optimization of this nanotechnology's CNS mobility can enable faster and more effective development of therapeutics for these disorders. A vital step towards finding effective therapeutics is understanding how nanoparticles move in the brain, and how the chemical properties of nanoparticles affect the effective diffusion.

Effective diffusion coefficient (D_{eff}) calculation

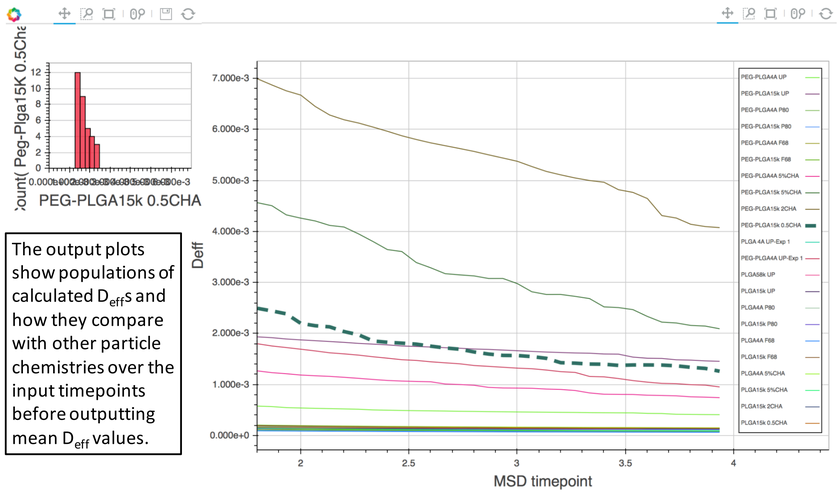
Effective diffusion coefficient (D_{eff}) is a useful measure of the ability of a nanoparticle to penetrate brain tissue and therefore overcome the blood-brain barrier. Diffusibility is experimentally assessed in *ex vivo* rat brain tissue through mean-squared diffusion (MSD) measurement, with a simple calculation then generating D_{eff}:

$$D_{eff} = \frac{MSD}{4 * t^{\alpha}}$$

By convention, t is taken to be 1 second to allow the particles enough diffusion time. In this analysis, we sought to account for potential effects of t-values on diffusion differences between particle chemistries. Therefore, a bokeh-dependent Python function was developed to visualize particle-chemistry-specific D_{eff}s from an input range of MSD timepoints and provide mean D_{eff} values for each chemistry.

Particle chemistry	Deff
PEG-PLGA4A UP	0.000473
PEG-PLGA15k UP	0.001681
PEG-PLGA4A P80	0.000088
PEG-PLGA15k P80	0.000086
PEG-PLGA4A F68	0.000099
PEG-PLGA15k F68	0.000096
PEG-PLGA4A 5%CHA	0.000960
PEG-PLGA15k 5%CHA	0.003086
PEG-PLGA15k 2CHA	0.005413
PEG-PLGA15k 0.5CHA	0.001667
PLGA 4A UP-Exp 1	0.000136
PEG-PLGA4A UP-Exp 1	0.001331
PLGA58k UP	0.000136
PLGA15k UP	0.000135
PLGA4A P80	0.000146
PLGA15k P80	0.000121
PLGA4A F68	0.000072
PLGA15k F68	0.000142
PLGA4A 5%CHA	0.000171
PLGA15k 5%CHA	0.000109
PLGA15k 2CHA	0.000157
PLGA15k 0.5CHA	0.000158

```
In [13]: time_variable_Deff.compute_plot_all_Deff(1.8,4,'PEG-PLGA15k 0.5CHA')
```



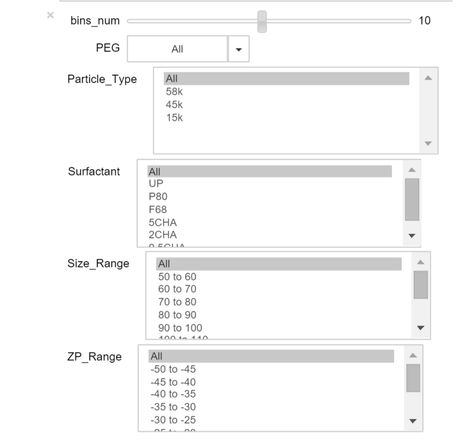
The output plots show populations of calculated D_{eff}s and how they compare with other particle chemistries over the input timepoints before outputting mean D_{eff} values.

D_{eff} comparison by nanoparticle chemistry

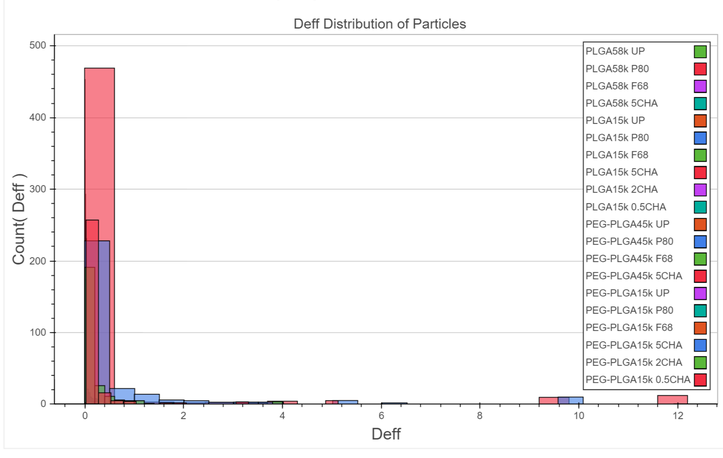
For analyzing the effective diffusion of particles, we started with experimental effective diffusion data of 6709 particles calculated at t=1 second from the 20 different particle chemistries. As done previously, organizing this data manually to visualize and decipher meaningful trends was laborious and inefficient.

Bokeh was used to explore the relations between nanoparticle chemistries and diffusion rates for the 20 nanoparticle formulations with histograms.

With interactive features, the output from a single call of the "interact_plot_deff" function allows the user to choose whichever nanoparticles to display, based on the size of abscissa bins, whether the particles are PEGylated, PLGA particle type, surfactant, categorical size ranges, and categorical zeta potential ranges.



An example of the histogram produced with all nanoparticle chemistries included is displayed below.

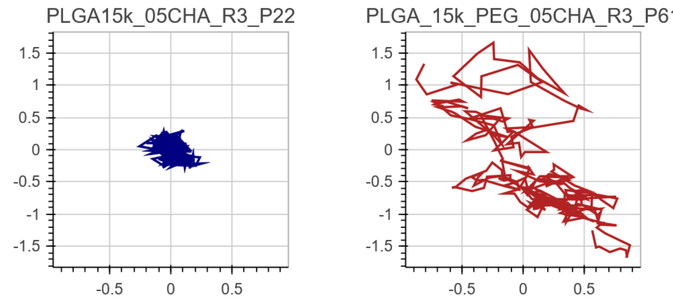


Particle trajectory visualization and comparison

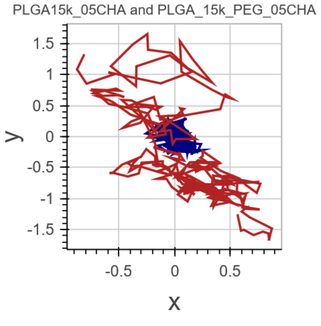
Rationale: Plots are an easy way of quickly evaluating and comparing the behavior of particles. Plots give an idea of the comparative magnitude of diffusion coefficients, distinguish diffusion from convection and other flow patterns, and aids in identifying errors in instrumentation.

Bokeh was used to develop interactive plots within an iPython notebook. Bokeh provides built-in toolbars, and output can easily be used to generate HTML code to embed in a website.

Functions were written to compare trajectory data side-by-side:



as well as in an overlay format:



Bokeh was also used to develop animated videos of particle trajectories. This is much more compact than large video files that are regularly used in presentations of particle diffusion.

* These authors contributed equally to this work.