MFI–Kinetic Technologies

Non-Confidential Summary

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This document summarizes investigational technologies under development by MultiFunctional Imaging, LLC. The technologies described herein are investigational, and they are not available for sale or for use as part of a medical device or product. This information is intended to educate potential investors and the scientific community about ongoing technology developments, and to obtain preliminary feedback from these groups and future potential users.

Overview

MFI–Kinetic Technologies comprise patent-pending algorithms and related techniques under development for general purpose compartment modeling that combine proven fitting routines with the new state-of-the-art technique: Reduced Parameter Space Kinetic Modeling(patent pending). The extensive library of technologies includes numerous techniques for simulating and fitting a variety of compartment models for applications such as quantitative tumor characterizations, quantification of myocardial blood flow, and numerous neurological applications.

All MFI–Kinetic Technologies support both single-tracer and multi-tracer kinetic modeling, providing core multi-tracer modeling for MFI–Cardiac Technologies and MFI–Oncology Technologies.

Features

Blood Input Function Modeling

- Model instantaneous samples or samples from image (integrated timeframes)
- Optional parameterization of arterial input and whole-blood curves [1, 2]
- Interpolation, extrapolation, and metabolite correction procedures
- Fractional blood volumes (f_B)
- Blood arrival time “delay” included in fits

Time-Activity Curve Modeling

- 1K-5K serial compartment models, adaptable to other models
  - 1-, 2-, and 3-tissue compartments with 1-5 rate parameters (K_1,k_2-k_5)
- Optional inclusion of whole-blood term (f_B) and blood arrival time delay
- Constrain every parameter to user-defined ranges

Reduced Parameter Space Kinetic Modeling Fits

- Natively-coded Reduced Parameter Space Kinetic Modeling formulations [3-7]
- Exhaustive search fits – guarantees true global-minimum fit to specified precision
  - Single-threaded fits in 10ms for 2K-3K models, 1sec for 4K-5K models[1]
- Ultra-fast Levenberg-Marquardt fits for voxelwise parametric imaging
  - Single-threaded fits in approx. 1ms for 2K-3K and 7ms for 4K-5K models[1]

Conventional Kinetic Modeling Algorithms

- Conventional non-linear least squares (NLLS) with Levenberg-Marquardt
- Simulated annealing to escape local minima
- Generalized linear least squares (GLLS)

Additional Features

- Patlak graphical analysis for trapped tracers (3K model)
- Logan graphical analysis(pending) for reversibly bound tracers (4K model)
- Computation of kinetic macroparameters (V_D, K_{net})
- Highly structured and organized C code optimized for computational efficiency
- Multi-threaded code for powerful parallelization

[1] Actual fitting times may vary depending on processor and data properties

Descriptions

Reduced Parameter Space Kinetic Modeling

The new state-of-the-art for compartment modeling, this technique greatly simplifies the mathematical fitting equations without making any assumptions, approximations, or manipulations of the data. The technique is based on three core principals:

1) Reformulating the kinetic modeling equations to maximally separate the linear and non-linear aspects of the problem.

2) Constraining the solution space to only include solutions that minimize the fitting objective function *in the linear sense*. In effect, the linear aspects of the fit are solved analytically—providing immediate best-fit linear parameters with little computation.

3) Employing robust fitting algorithms to solved the reduced nonlinear fitting problem. Only the nonlinear parameters need to be fitted here, resulting in only a 1D (2K-3K models) or 2D (4K-5K models) non-linear fit—*greatly simplifying the nonlinear fit*.

Application of the Reduced Parameter Space Kinetic Modeling technique greatly reduces the dimensionality of the nonlinear compartment model fitting problem as shown in Table 1. This results in a much smaller nonlinear fitting problem, reduced to only 1 or 2 free parameters, that can be solved much faster and more robustly than conventional fits in up to 6 free parameters.

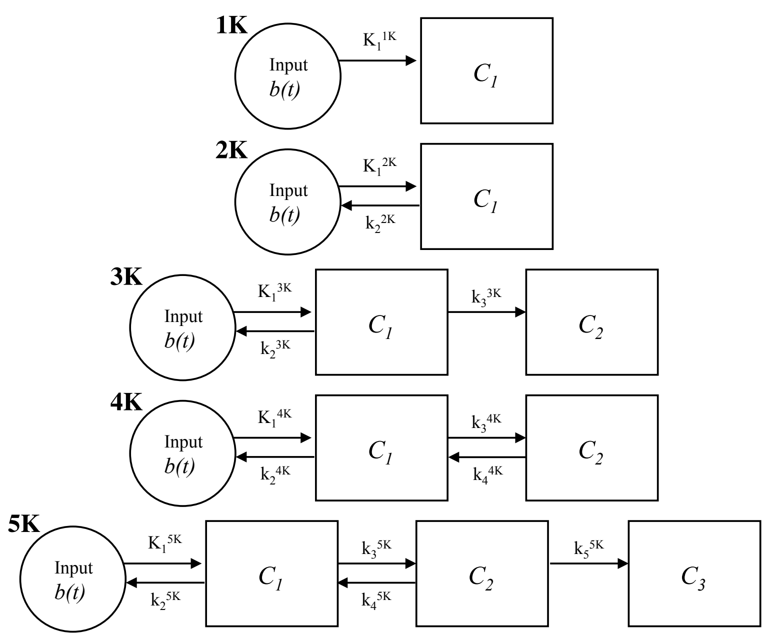

Figure 1. Serial compartment models consisting of an arterial input *b(t)* that drives 1-3 tissue compartments. Kinetic rate parameters K_1, k_2-k_5 describe directional exchange between the compartments.

Table 1. Complexity of Fitting Problems

	Conventional Modeling		Reduced Parameter Space	
Model	**Fitting Dimension**	**Parameters in Nonlinear Fit**	**Nonlinear Fitting Dimension**	**Parameters in Nonlinear Fit**[1]
1K no f_B	1[2]	K_1	0	NA
with f_B	2	f_B, K_1	0	NA
2K no f_B	2	K_1, k_2	1	υ_1
with f_B	3	f_B, K_1, k_2	1	υ_1
3K no f_B	3	K_1, k_2, k_3	1	υ_1
with f_B	4	f_B, K_1, k_2, k_3	1	υ_1
4K no f_B	4	K_1, k_2, k_3, k_4	2	υ_1, υ_2
with f_B	5	f_B, K_1, k_2, k_3, k_4	2	υ_1, υ_2
5K no f_B	5	K_1, k_2, k_3, k_4, k_5	2	υ_1, υ_2
with f_B	6	f_B, K_1, k_2, k_3, k_4, k_5	2	υ_1, υ_2

[1] The linear parameters in the reformulated equations are solved analytically, and do not complicate the nonlinear fit.
[2] The 1K model without f_B is inherently a linear fitting problem

Fitting Algorithms

Conventional Levenberg-Marquardt

Provides iterative non-linear least-squares (NLLS) fits for conventional model formulations. The utility of conventional NLLS is largely replaced by the Reduced Parameter Space Kinetic Modeling algorithms. The conventional LM algorithm is included with MFI–Kinetic Technologies for historical comparison purposes.

Conventional Simulated Annealing

Conventional NLLS suffers from many shortcomings, including sensitivity to initial conditions that results in the algorithm converging to the closest local minimum. Simulated annealing offers a means to escape local minima and converge (at least population sense) toward the true global minimum. Conventional simulated annealing is included with MFI–Kinetic Technologies for historical comparison purposes.

Exhaustive Search for Reduced Parameter Space

The Reduced Parameter Space reformulations reduced the size of the nonlinear fitting problem so that the *entire* solution space can be rapidly and exhaustively searched to guarantee identification of the true global minimum to user-defined search precision. These fits can be configured to be equivalent to published basis functions methods [8, 9] as desired. MFI–Kinetic Technologies provides extremely fast and robust exhaustive search fits, fitting 2K-3K models to a precision of 0.001 min^{-1} in approximately 10ms, and 4K-5K models in approximately 1 sec for single-threaded code. Multi-threading can reduce these times by an order of magnitude.

Levenberg-Marquardt for Reduced Parameter Space

MFI–Kinetic Technologies also includes state-of-the-art techniques for using iterative Levenberg-Marquardt with the Reduced Parameter Space reformulations to provide ultra-fast and robust fits. The reduced dimensionality of offered by this approach overcomes the main limitations of conventional NLLS by largely suppressing local minima and greatly reducing sensitivity to initial conditions. Single-threaded fits require as little as 1ms and 7ms for 2K-3K and 4K-5K models, respectively, enabling full compartment model fits to every image voxel in only minutes of CPU time.

Full Control over User-Defined Constraints

Many accelerated kinetic modeling algorithms introduce data transformations or make other assumptions that limit the user's ability to control and constrain fit results. MFI–Kinetic Technologies provides complete control over the fitted parameters. Each parameter can be fully unconstrained, constrained to be non-negative, constrained to fall within a user-defined [min,max] range, or set to a pre-determined value.

References

[1] D. Feng, S. C. Huang, and X. Wang, "Models for computer simulation studies of input functions for tracer kinetic modeling with positron emission tomography," *Int J Biomed Comput,* 32(3):95-110, 1993.

[2] J. A. Thompson, F. Starmar, R. E. Whalen, and H. D. McIntosh, "Indicator transit time considered as a gamma variate," *Circ Res,* 14:502-515, 1964.

[3] D. J. Kadrmas and M. B. Oktay, "Fast Voxelwise Compartment Modeling for Parametric Imaging," *J Nucl Med,* 53(5S):2301, 2012.

[4] D. J. Kadrmas and M. B. Oktay, "Rapid Multi-Tracer PET using Reduced Parameter Space Kinetic Modeling," in *IEEE Nuclear Science Symposium and Medical Imaging Conference*, 2012, in press.

[5] D. J. Kadrmas and M. B. Oktay, "Reduced Parameter Space Formulations for Fast and Robust Kinetic Modeling," *Phys Med Biol,* submitted 2012.

[6] M. B. Oktay and D. J. Kadrmas, "Reduced Parameter Space Formulations for Robust Kinetic Modeling," *J Nucl Med,* 53(5S):2292, 2012.

[7] M. B. Oktay and D. J. Kadrmas, "Fast Iterative Nonlinear Algorithms for Reduced Parameter Space Kinetic Modeling," in *IEEE Nuclear Science Symposium and Medical Imaging Conference*, 2012, in press.

[8] Y. T. Hong, J. S. Beech, R. Smith, J. C. Baron, and T. D. Fryer, "Parametric mapping of [18F]fluoromisonidazole positron emission tomography using basis functions," *J Cereb Blood Flow Metab,* 31(2):648-57, 2011.

[9] Y. T. Hong and T. D. Fryer, "Kinetic modelling using basis functions derived from two-tissue compartmental models with a plasma input function: general principle and application to [18F]fluorodeoxyglucose positron emission tomography," *Neuroimage,* 51(5):164-72, 2010.

About MULTIFUNCTIONAL IMAGING

MFI is developing state-of-the-art technologies for advanced medical imaging applications, targeting streamlined solutions for obtaining and quantifying multiple imaging results in a single scan. Founded in November 2011, MFI is based on several patented and patent-pending technologies developed in cooperation with the University of Utah. These technologies include systems and methods for single-scan dual-state rest+stress myocardial perfusion PET imaging (MFI–Cardiac Technologies), single-scan multi-tracer PET imaging for quantification and assessment of multiple aspects of tumor function (MFI–Oncology Technologies), and fast and robust kinetic modeling for analysis of dynamic imaging data (MFI–Kinetic Technologies). MFI's Founder and Chief Science Officer is Dan J. Kadrmas, Ph.D., who also holds appointments as Tenured Professor in the Utah Center for Advanced Imaging Research (UCAIR), Department of Radiology, and as Associate Director–PET Physics, Molecular Imaging Program, Huntsman Cancer Institute at the University of Utah. The Chief Executive Officer, Dave Dolan, MBA, possesses a broad professional background in developing service programs for diagnostic imaging clients. He has over 18 years of experience with executive roles at GE Healthcare, GE Capital, SPX Corp and Becton Dickinson.

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