Supplemental: Supervised Machine Learning for Predicting Drug Release from Acetalated Dextran Nanofibers

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Supplementary Contents:

Supplementary Figures:

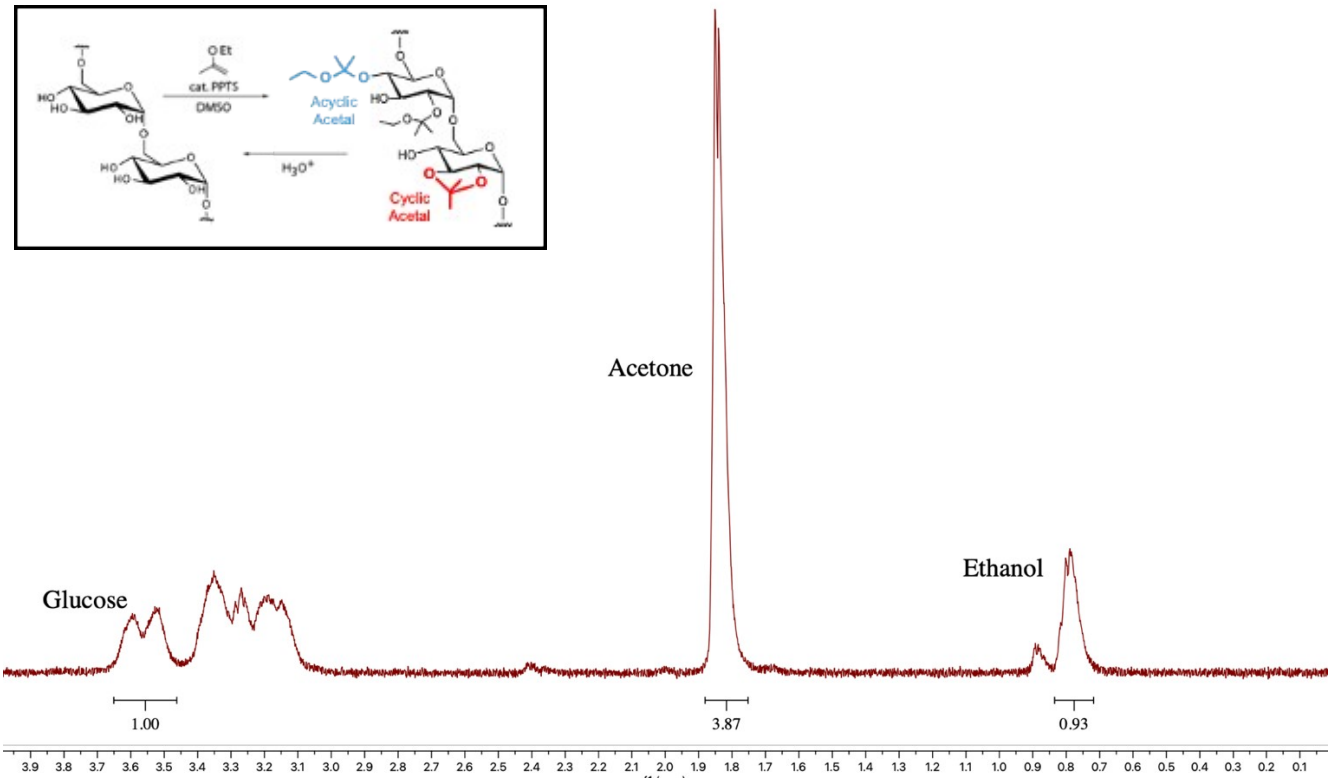

Figure S1: Ace-DEX H-NMR Spectrum. 51.6% CAC Ace-DEX synthesized from dextran with a reaction time of 14 minutes. Each peak labeled and integrated via ^{1}H-NMR (Varian Inova 400 MHz) of Ace-DEX degraded in deuterated water with 10% v/v deuterated hydrochloric acid (Sigma). Inlet picture is a schematic of dextran (left) to Ace-DEX (right) synthesis reaction. Et. = Ethyl group; cat. PPTS = catalyst pyridinium p-toluenesulfonate; DMSO = dimethylsulfoxide.

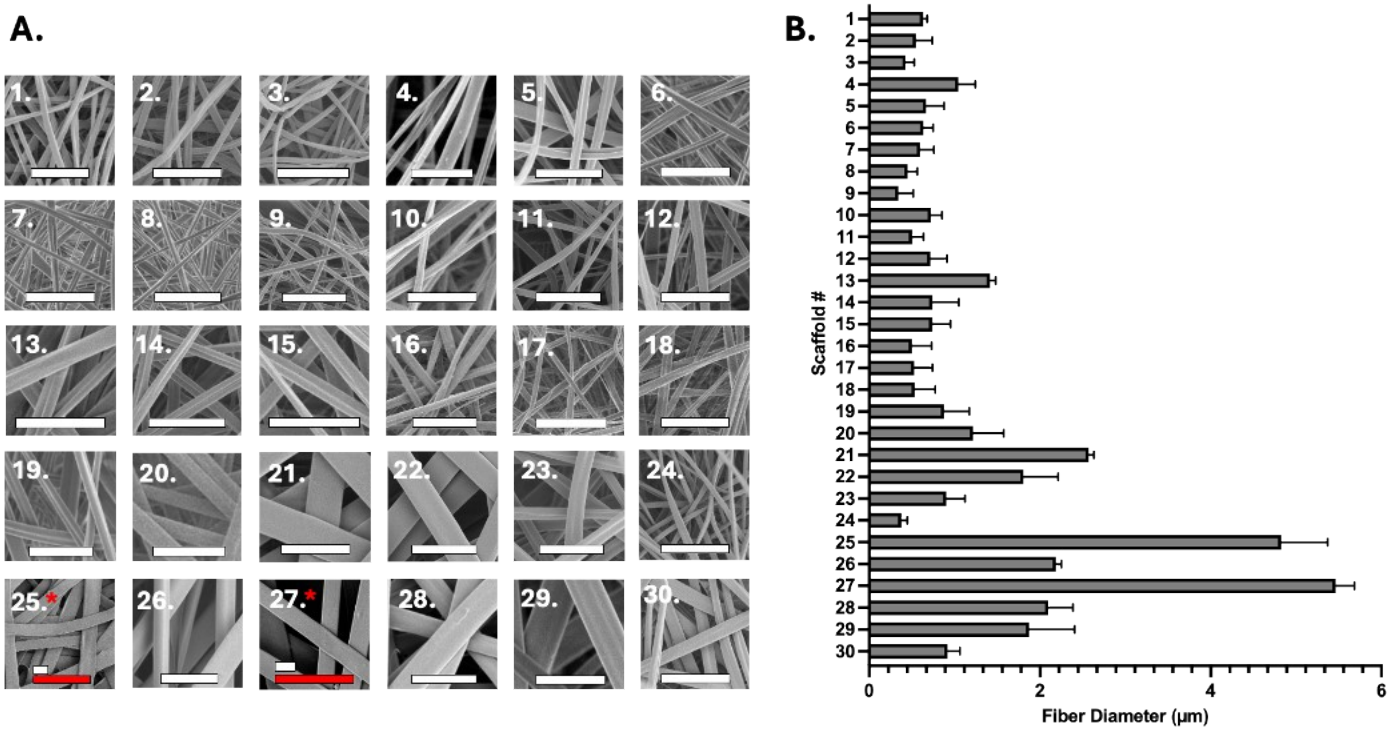

Figure S2: Drug-loaded electrospun Ace-DEX scaffolds. (**A**) Representative scanning electron microscopy (SEM) images of the thirty monoaxial scaffolds included in model development. Images are labeled according to the scaffold # (Table S1). All white scale bars are 5µm. *Scaffold 25 & 27 red scale bar = 20µm. (**B**) Average fiber diameter for each scaffold with n ≥ 30 measurements via ImageJ software. Error bars are ± standard deviation.

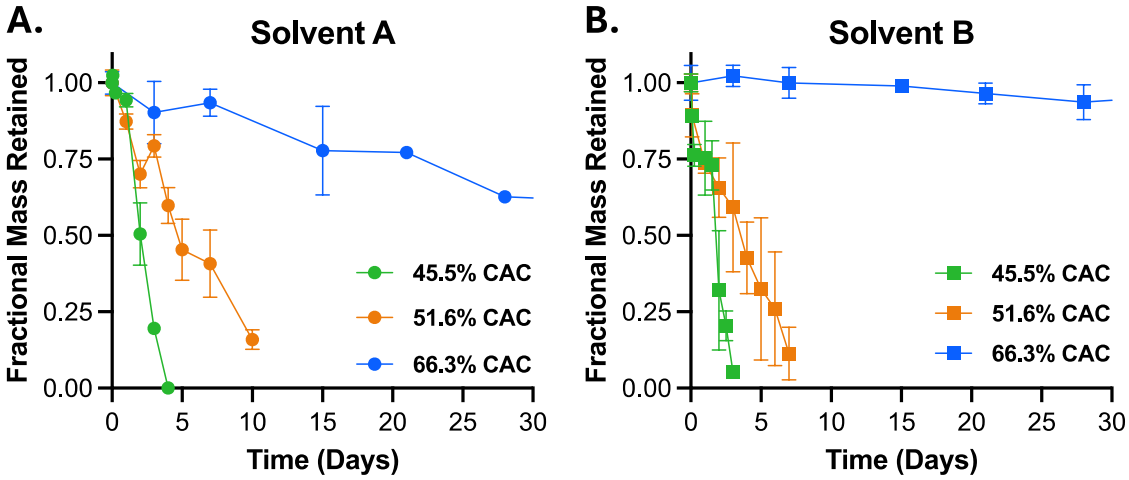

Figure S3: Blank Ace-DEX Scaffold Degradation. In vitro fractional mass versus time of blank monoaxial scaffolds electrospun in (**A**) solvent system A, hexafluoro-2-propanol (HFIP):1-butanol [60:40, v/v] with 1% TEA, and (**B**) solvent system B, dichloromethane:HFIP:1-butanol [30:30:40, v/v/v]. Fractional mass retained was calculated using Supp. Eq. 2. Individual points represent the average of technical replicates with error bars as ± standard deviation.

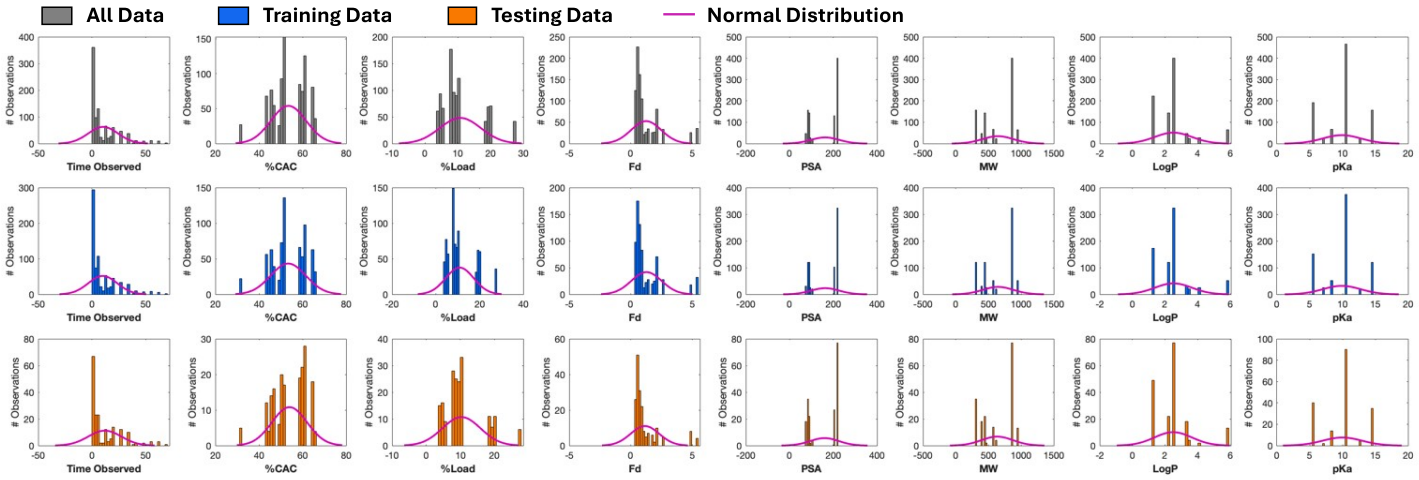

Figure S4: Histograms of the data sets used in ML model development. Three by eight plot matrix where each row represents (from top to bottom) all data, training data, and testing data, respectively. Matrix is organized in columns with respect to one of the eight parameters initially included in building the model. Each histogram shows a pink line capturing the normal distribution of all observations (y-axis) across the respective parameter values (x-axis) within the given dataset.

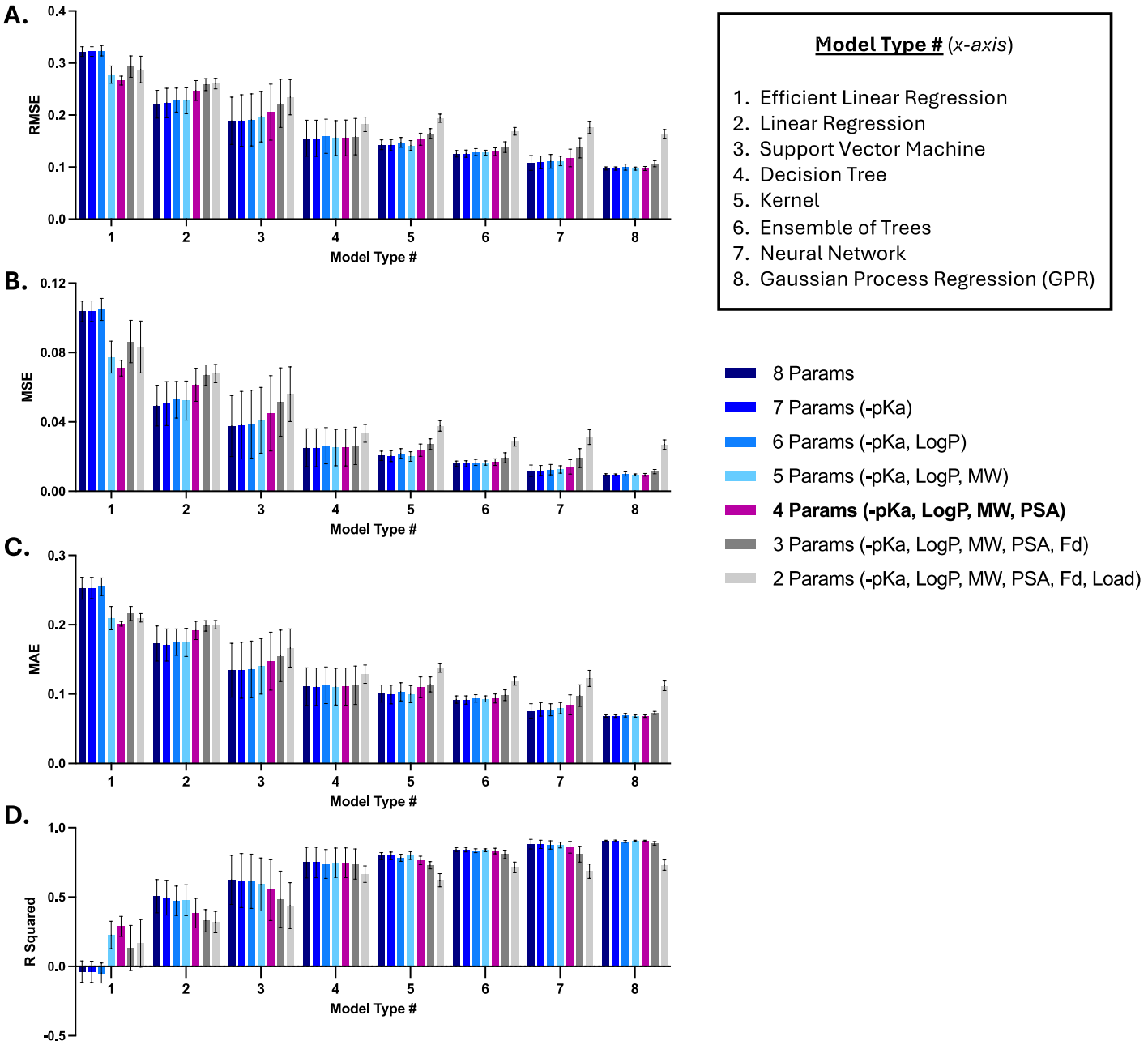

Figure S5: Assessment of ML models following parameter reduction. Pooled average training and testing performance metrics including (**A**) root mean squared error (RMSE), (**B**) mean squared error (MSE), (**C**) mean absolute error (MAE), and (**D**) R squared for different parametrized simulations. Model type labeled by # along x-axis corresponding to the inset list. Simulations are distinguished by the total number of parameters (params) that were included. Parameters removed for each are shown in parentheses of the legend. Error bars ± standard deviation.

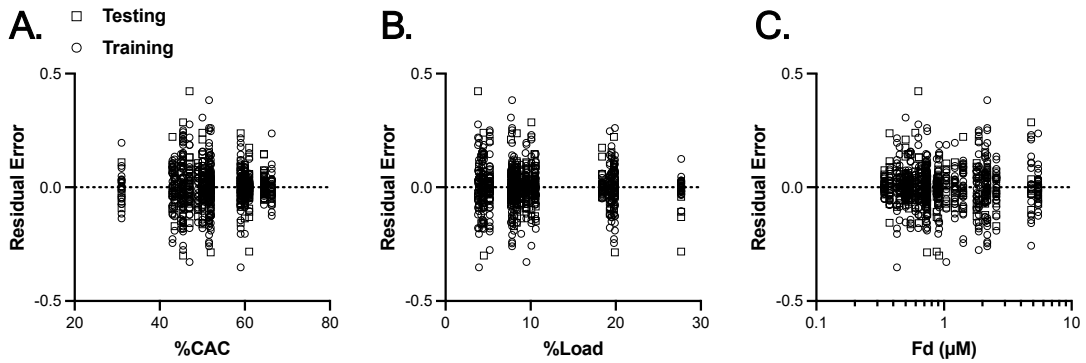

Figure S6: Error associated to training and testing parameters. Residual errors associated to the training and testing F(t) GPR model predictions plotted against the parameters (**A**) % CAC, (**B**) %Load, and (**C**) Fd.

A.

Data (n=)	ALL DATA (n=929)			AVG DATA (n=276)		
ERROR:	MAE	MSE	RMSE	MAE	MSE	RMSE
"ALL"	0.084	0.058	0.007	0.056	0.034	0.003
DXR	0.124	0.091	0.015	0.101	0.071	0.010
ERL	0.075	0.052	0.006	0.046	0.037	0.002
EVR	0.074	0.056	0.005	0.062	0.047	0.004
PTX	0.066	0.044	0.004	0.049	0.025	0.002
RESI	0.070	0.054	0.005	0.032	0.026	0.001
RBC	0.105	0.075	0.011	0.060	0.035	0.004
SFN	0.143	0.119	0.020	0.092	0.076	0.009
TRM	0.113	0.082	0.013	0.042	0.028	0.002

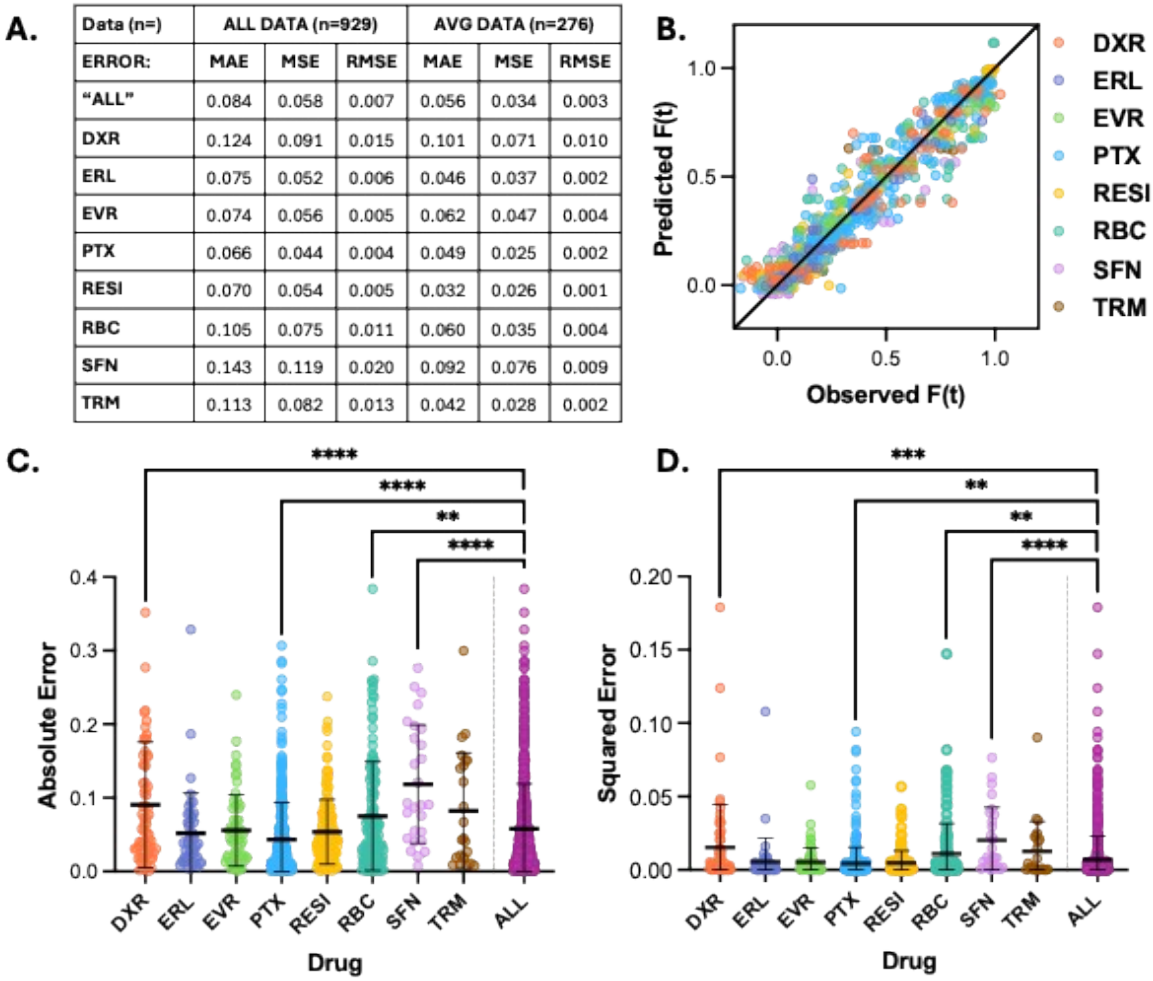

Figure S7: Error metrics for GPR predictions with respect to drug (**A**) Table showing the error metrics for the compiled data sets including "ALL" (n=929 observations, Supp. File 1) and "AVG" (n=276 observations, Supp. File 4). Errors including MAE, mean absolute error; MSE, mean squared error; and RMSE, root mean squared error listed for combined predictions ("ALL") and predictions grouped by drugs. (**B**) Scatter plot for predicted versus observed F(t) for the full 929 observations grouped by drug. Black diagonal line represents the identity for perfect predictions. (**C**) Absolute error and (**D**) squared error for the 929 predictions ("ALL") and predictions corresponding to specific drugs. Black bars represent the MAE and MSE for each group in (C) and (D), respectively. Error bars are ± standard deviation of the means. **p<0.01, ****p<0.0001 by two-tailed, unpaired t-test between means.

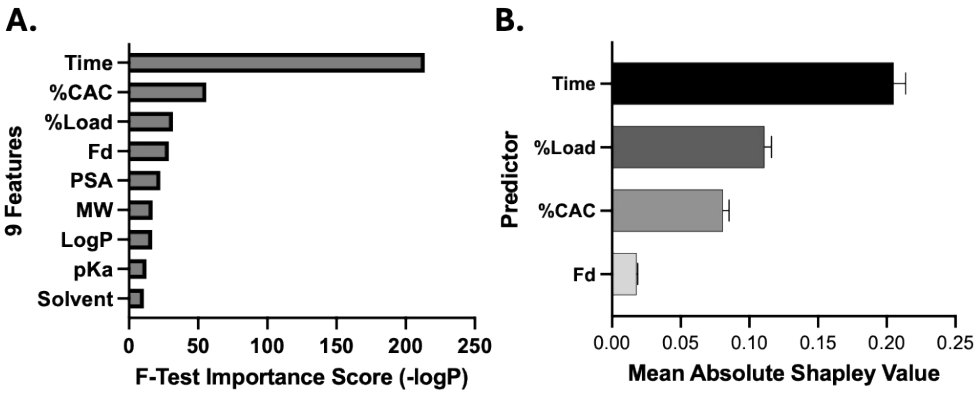

Figure S8: Feature Importance Rankings. (A) F-Test (-logP) importance scores taken from MATLAB Regression Learner simulations from 929 observations. (**B**) Mean absolute Shapley values for only GPR model predictions where the scaffold parameter *%Load* was less than 5% (wt. drug). Error bars are ± standard error of the mean.

Supplementary Tables:

Table S1: Electrospun Ace-DEX Scaffolds. Release data used for model development from the thirty scaffolds included in table. Parameters including the encapsulated drug, monoaxial solvent system, drug molecular weight (MW), partition coefficient (LogP), polar surface area (PSA), pKa, Ace-DEX %CAC, drug loading (%Load, wt./wt.), and fiber diameter (Fd, μm) are defined for each scaffold. Solvent system A = hexafluoro-2-propanol (HFIP):1-butanol [60:40, v/v] with 1% TEA. Solvent system B = dichloromethane:HFIP:1-butanol [30:30:40, v/v/v].

Scaffold ID #	Drug Name	Drug ID	Solvent	MW[a] (g/mol)	LogP[a]	PSA[a] (Å)	pKa[b]	%CAC	%Load[c] (wt.)	Fd[d] (μm)
1	Doxorubicin HCl	DXR	A	579.15	1.27	206	8.2	47	3.81	0.630
2	Doxorubicin HCl	DXR	A	579.15	1.27	206	8.2	50	4.32	0.548
3	Doxorubicin HCl	DXR	A	579.15	1.27	206	8.2	59	3.93	0.428
4	Erlotinib	ERL	A	393.4	3.3	74.7	5.42	47	9.52	1.042
5	Erlotinib	ERL	A	393.4	3.3	74.7	5.42	50	10.5	0.664
6	Everolimus	EVR	A	958.2	5.9	205	10.4	47	4.20	0.635
7	Everolimus	EVR	A	958.2	5.9	205	10.4	50	4.46	0.595
8	Everolimus	EVR	A	958.2	5.9	205	10.4	59	4.42	0.449
9	Paclitaxel	PTX	A	853.9	2.5	221	10.4	64.5	5.20	0.341
10	Paclitaxel	PTX	A	853.9	2.5	221	10.4	45	10.6	0.723
11	Paclitaxel	PTX	A	853.9	2.5	221	10.4	50	7.68	0.500
12	Paclitaxel	PTX	A	853.9	2.5	221	10.4	60	8.22	0.715
13	Paclitaxel	PTX	A	853.9	2.5	221	10.4	43	19.8	1.413
14	Paclitaxel	PTX	A	853.9	2.5	221	10.4	52	19.3	0.739
15	Paclitaxel	PTX	A	853.9	2.5	221	10.4	52	19.9	0.737
16	Paclitaxel	PTX	A	853.9	2.5	221	10.4	61	18.4	0.499
17	Paclitaxel	PTX	A	853.9	2.5	221	10.4	64.5	10.5	0.526
18	Paclitaxel	PTX	A	853.9	2.5	221	10.4	61	9.40	0.533
19	Paclitaxel	PTX	A	853.9	2.5	221	10.4	61	27.7	0.876
20	Resiquimod	RESI	B	314.4	1.3	86.2	14.63	31	9.49	1.215
21	Resiquimod	RESI	B	314.4	1.3	86.2	14.63	43.5	8.05	2.570
22	Resiquimod	RESI	B	314.4	1.3	86.2	14.63	49	8.40	1.805
23	Resiquimod	RESI	B	314.4	1.3	86.2	14.63	60	8.88	0.901
24	Resiquimod	RESI	A	314.4	1.3	86.2	14.63	59	8.38	0.375
25	Ribociclib	RBC	B	434.5	2.2	91.2	5.5	45.5	10.1	4.828
26	Ribociclib	RBC	B	434.5	2.2	91.2	5.5	51.6	7.82	2.186
27	Ribociclib	RBC	B	434.5	2.2	91.2	5.5	66.3	7.79	5.463
28	Ribociclib	RBC	B	434.5	2.2	91.2	5.5	51.6	19.5	2.099
29	Sorafenib	SFN	A	464.8	4.1	92.4	7.2	45.5	5.20	1.871
30	Trametinib	TRM	A	615.4	3.4	102	12.6	45.5	4.50	0.917

[a]MW, LogP, and PSA were extracted from PubChem and [b]pKa was extracted from DrugBank or PubChem
[c]%Load determined in vitro and averaged from technical replicates using equation 1
[d]Fd is the average of ≥ 30 measurements of scanning electron microscopy images using ImageJ software

Table S2: MATLAB Regression Learner machine learning models trained and tested. The 28 models included in the Regression Learner Application and grouped according to model type (IDs A-H). Performance metrics from the training and testing of each model with the designated data. '8 parameters' includes drug + scaffold-specific parameters and '4 parameters' includes only scaffold-specific parameters. Highlighted model (Gaussian process regression) indicates the best performing type across 8 and 4 parameters identified in **Fig. 2.**

TABLE S2	8 PARAMETERS	4 PARAMETERS

				TRAINING				TESTING				TRAINING				TESTING			
#	Type	ID	*Model Name*	MAE	MSE	RMSE	R^2	MAE	MSE	RMSE	R^2	MAE	MSE	RMSE	R^2	MAE	MSE	RMSE	R^2
1	**Efficient Linear Regression**	**1A**	*Efficient Linear Least Squares*	0.272	0.105	0.324	-0.001	0.256	0.096	0.310	-0.003	0.204	0.067	0.259	0.358	0.204	0.069	0.262	0.281
		1B	*Efficient Linear SVM*	0.242	0.110	0.332	-0.050	0.249	0.110	0.332	-0.153	0.202	0.077	0.277	0.266	0.201	0.077	0.278	0.193
2	**Linear Regression**	**2A**	*Linear*	0.195	0.060	0.245	0.426	0.199	0.060	0.245	0.375	0.204	0.067	0.259	0.358	0.204	0.069	0.262	0.281
		2B	*Interactions Linear*	0.146	0.038	0.194	0.640	0.148	0.037	0.192	0.615	0.178	0.052	0.227	0.508	0.183	0.055	0.235	0.425
		2C	*Robust Linear*	0.194	0.061	0.246	0.420	0.197	0.060	0.246	0.370	0.201	0.070	0.264	0.335	0.208	0.075	0.275	0.212
		2D	*Stepwise Linear*	0.150	0.040	0.201	0.614	0.154	0.040	0.199	0.586	0.178	0.052	0.228	0.505	0.183	0.055	0.235	0.425
3	**Support Vector Machine (SVM)**	**3A**	*Linear SVM*	0.190	0.064	0.253	0.388	0.187	0.062	0.249	0.352	0.198	0.072	0.268	0.313	0.200	0.077	0.277	0.199
		3B	*Quadratic SVM*	0.136	0.036	0.188	0.661	0.127	0.033	0.183	0.652	0.158	0.049	0.222	0.531	0.162	0.051	0.225	0.471
		3C	*Cubic SVM*	0.105	0.022	0.149	0.788	0.090	0.015	0.124	0.839	0.121	0.029	0.169	0.727	0.125	0.029	0.171	0.696
		3D	*Fine Gaussian SVM*	0.084	0.016	0.126	0.848	0.085	0.016	0.125	0.836	0.083	0.015	0.123	0.856	0.081	0.014	0.119	0.851
		3E	*Medium Gaussian SVM*	0.120	0.030	0.173	0.714	0.115	0.028	0.168	0.706	0.130	0.035	0.186	0.669	0.132	0.036	0.191	0.620
		3F	*Coarse Gaussian SVM*	0.181	0.058	0.240	0.449	0.174	0.055	0.234	0.427	0.192	0.066	0.258	0.366	0.189	0.067	0.259	0.300
4	**Decision Tree**	**4A**	*Fine Tree*	0.083	0.015	0.123	0.856	0.080	0.013	0.114	0.863	0.082	0.015	0.122	0.858	0.080	0.013	0.115	0.862
		4B	*Medium Tree*	0.112	0.026	0.161	0.754	0.109	0.023	0.151	0.763	0.115	0.027	0.164	0.742	0.114	0.025	0.159	0.736
		4C	*Coarse Tree*	0.141	0.037	0.192	0.648	0.142	0.038	0.196	0.600	0.140	0.037	0.192	0.649	0.141	0.037	0.193	0.611
5	**Kernel**	**5A**	*SVM Kernel*	0.088	0.018	0.133	0.831	0.104	0.026	0.161	0.728	0.104	0.023	0.152	0.780	0.104	0.021	0.144	0.783
		5B	*Least Squares Regression Kernel*	0.118	0.024	0.156	0.766	0.112	0.023	0.151	0.761	0.121	0.026	0.162	0.751	0.123	0.027	0.163	0.723
6	**Ensemble of Trees**	**6A**	*Boosted Trees*	0.099	0.018	0.136	0.824	0.095	0.016	0.127	0.832	0.100	0.019	0.139	0.817	0.099	0.018	0.135	0.810
		6B	*Bagged Trees*	0.087	0.015	0.122	0.858	0.086	0.014	0.119	0.852	0.090	0.016	0.126	0.849	0.087	0.014	0.120	0.849
7	**Neural Network**	**7A**	*Narrow Neural Network*	0.085	0.015	0.121	0.861	0.101	0.019	0.138	0.800	0.110	0.022	0.147	0.792	0.097	0.016	0.128	0.828
		7B	*Medium Neural Network*	0.075	0.011	0.106	0.892	0.069	0.009	0.094	0.907	0.079	0.012	0.111	0.882	0.088	0.014	0.120	0.850
		7C	*Wide Neural Network*	0.068	0.010	0.098	0.908	0.066	0.009	0.093	0.910	0.070	0.011	0.103	0.899	0.073	0.012	0.110	0.874
		7D	*Bilayered Neural Network*	0.072	0.010	0.102	0.900	0.072	0.011	0.104	0.888	0.076	0.012	0.108	0.890	0.079	0.011	0.105	0.885
		7E	*Trilayered Neural Network*	0.070	0.010	0.101	0.902	0.070	0.009	0.095	0.906	0.076	0.012	0.108	0.888	0.071	0.009	0.096	0.903
8	**Gaussian Process Regression (GPR)**	**8A**	*Squared Exponential GPR*	0.069	0.010	0.099	0.906	0.071	0.010	0.099	0.897	0.069	0.010	0.099	0.906	0.069	0.009	0.097	0.902
		8B	*Matern 5/2 GPR*	0.068	0.010	0.098	0.908	0.070	0.010	0.098	0.900	0.069	0.010	0.099	0.906	0.068	0.009	0.096	0.904
		8C	*Exponential GPR*	0.065	0.009	0.095	0.914	0.066	0.008	0.091	0.913	0.066	0.009	0.096	0.912	0.065	0.008	0.091	0.913
		8D	*Rational Quadratic GPR*	0.066	0.009	0.096	0.911	0.067	0.009	0.095	0.906	0.067	0.010	0.098	0.909	0.066	0.009	0.093	0.909

MAE = mean absolute error; MSE = mean squared error; RMSE = root mean squared error; R^2 = goodness of fit

Table S3: Conventional models used for characterizing drug release vs. time. These models were adapted from literature to describe fractional drug release (F(t)) as a function of time, t, for the Ace-DEX scaffolds.

Model	**Adapted Equation F(t) =**	Reference**:**

Zero-Order	$k_0 \cdot t$	[1]
First-Order	$e^{k_1 \cdot t}$	[1]
Higuchi	$k_H \cdot t^{1/2}$	[1]
Korsmeyer-Peppas	$k_{KP} \cdot t^n$	[1]
Kopcha	$A \cdot t + B \cdot t^{1/2}$	[2]

k_0 = zero-order rate constant; k_1 = first-order rate constant; k_H = Higuchi rate constant; k_{KP} = Korsmeyer-Peppas rate constant; A / B = Kopcha equation coefficients.[1, 2]

Table S4: Performance metrics for GPR model predictions and conventional model simulations. Four scaffold-specific parameters used for GPR model predictions at each time point assessed for drug release in vitro. The in vitro data for each scaffold was used to solve for the constants and predict time-associated release for the conventional models including zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Kopcha. Error and goodness of fit was determined between model predictions and the average released in vitro from time-matched technical replicates.
MAE = mean absolute error; MSE = mean squared error; RMSE = root mean squared error; R^2 = goodness of fit.

Scaffold #	GPR				Zero-Order				First-Order				Higuchi				Korsmeyer-Peppas				Kopcha			
	MAE	MSE	RMSE	R^2	MAE	MSE	RMSE	R^2	MAE	MSE	RMSE	R^2	MAE	MSE	RMSE	R^2	MAE	MSE	RMSE	R^2	MAE	MSE	RMSE	R^2
1	0.107	0.021	0.146	0.783	0.174	0.038	0.194	0.619	0.073	0.013	0.115	0.866	0.116	0.025	0.159	0.743	0.013	0.000	0.014	0.966	0.117	0.019	0.139	-2.513
2	0.059	0.006	0.075	0.940	0.092	0.012	0.111	0.870	0.089	0.013	0.116	0.858	0.068	0.007	0.083	0.928	0.053	0.004	0.066	0.920	0.064	0.005	0.074	0.900
3	0.058	0.007	0.081	0.828	0.101	0.016	0.126	0.583	0.195	0.051	0.227	-0.352	0.173	0.039	0.197	-0.016	0.041	0.003	0.051	0.774	0.119	0.020	0.141	-0.717
4	0.052	0.004	0.061	0.946	0.069	0.006	0.080	0.907	0.087	0.020	0.142	0.707	0.145	0.029	0.171	0.580	0.089	0.016	0.125	0.752	0.081	0.008	0.090	0.872
5	0.025	0.001	0.029	0.989	0.027	0.001	0.031	0.987	0.078	0.011	0.105	0.854	0.098	0.015	0.124	0.795	0.061	0.006	0.076	0.921	0.029	0.001	0.034	0.984
6	0.048	0.004	0.060	0.967	0.054	0.003	0.057	0.970	0.050	0.004	0.064	0.963	0.063	0.008	0.087	0.931	0.022	0.001	0.029	0.987	0.026	0.001	0.029	0.986
7	0.041	0.004	0.059	0.950	0.033	0.002	0.040	0.977	0.037	0.003	0.055	0.957	0.056	0.005	0.072	0.926	0.026	0.001	0.030	0.981	0.020	0.001	0.024	0.988
8	0.050	0.004	0.064	0.961	0.029	0.001	0.035	0.988	0.039	0.004	0.059	0.967	0.093	0.012	0.110	0.886	0.022	0.001	0.024	0.994	0.021	0.000	0.022	0.995
9	0.009	0.000	0.011	0.995	0.018	0.001	0.024	0.977	0.040	0.002	0.048	0.907	0.051	0.004	0.064	0.833	0.041	0.002	0.049	0.898	0.019	0.000	0.022	0.980
10	0.043	0.003	0.051	0.971	0.046	0.003	0.051	0.971	0.096	0.014	0.118	0.846	0.093	0.015	0.121	0.835	0.056	0.004	0.060	0.940	0.042	0.002	0.050	0.959
11	0.017	0.001	0.029	0.986	0.018	0.000	0.020	0.994	0.059	0.006	0.075	0.909	0.108	0.016	0.128	0.737	0.018	0.001	0.023	0.987	0.023	0.001	0.026	0.984
12	0.024	0.001	0.029	0.986	0.025	0.001	0.035	0.928	0.030	0.002	0.041	0.903	0.026	0.001	0.029	0.951	0.028	0.001	0.034	0.902	0.020	0.001	0.027	0.939
13	0.111	0.023	0.152	0.833	0.072	0.009	0.095	0.935	0.144	0.047	0.217	0.657	0.157	0.040	0.199	0.712	0.080	0.013	0.114	0.876	0.082	0.010	0.098	0.908
14	0.027	0.001	0.035	0.987	0.044	0.003	0.050	0.974	0.098	0.013	0.114	0.866	0.159	0.030	0.174	0.688	0.050	0.005	0.074	0.926	0.037	0.002	0.044	0.974
15	0.023	0.001	0.033	0.990	0.077	0.012	0.110	0.896	0.105	0.017	0.130	0.853	0.159	0.032	0.179	0.723	0.143	0.046	0.215	0.555	0.081	0.010	0.101	0.901
16	0.015	0.001	0.035	0.938	0.017	0.000	0.021	0.977	0.037	0.002	0.050	0.870	0.073	0.007	0.085	0.626	0.036	0.004	0.060	0.815	0.020	0.001	0.026	0.965
17	0.015	0.000	0.021	0.989	0.023	0.001	0.031	0.976	0.069	0.007	0.085	0.824	0.073	0.008	0.087	0.815	0.032	0.003	0.052	0.911	0.026	0.001	0.031	0.976
18	0.007	0.000	0.009	0.997	0.032	0.002	0.042	0.933	0.036	0.005	0.069	0.821	0.097	0.012	0.108	0.564	0.022	0.001	0.033	0.960	0.043	0.003	0.053	0.898
19	0.022	0.001	0.035	0.949	0.045	0.003	0.053	0.888	0.045	0.006	0.077	0.758	0.097	0.013	0.114	0.478	0.064	0.013	0.113	0.495	0.047	0.004	0.060	0.858
20	0.022	0.001	0.025	0.996	0.191	0.045	0.211	0.706	0.051	0.005	0.067	0.970	0.096	0.017	0.130	0.889	0.115	0.025	0.157	0.805	0.107	0.019	0.136	0.853
21	0.024	0.001	0.028	0.993	0.057	0.005	0.070	0.953	0.180	0.063	0.251	0.403	0.119	0.021	0.147	0.797	0.080	0.013	0.113	0.872	0.060	0.006	0.076	0.941
22	0.035	0.002	0.044	0.972	0.049	0.003	0.055	0.956	0.072	0.008	0.088	0.887	0.057	0.005	0.068	0.932	0.092	0.012	0.109	0.803	0.050	0.004	0.063	0.933
23	0.025	0.001	0.029	0.811	0.035	0.002	0.046	0.514	0.070	0.007	0.082	-0.567	0.062	0.005	0.073	-0.223	0.040	0.002	0.047	0.336	0.051	0.003	0.059	-0.068
24	0.026	0.001	0.035	0.767	0.024	0.001	0.028	0.852	0.023	0.001	0.037	0.746	0.015	0.001	0.024	0.895	0.017	0.001	0.025	0.853	0.017	0.001	0.025	0.856
25	0.106	0.015	0.122	0.907	0.088	0.012	0.110	0.924	0.108	0.025	0.157	0.846	0.140	0.029	0.169	0.820	0.120	0.029	0.172	0.796	0.091	0.010	0.100	0.931
26	0.024	0.002	0.040	0.984	0.193	0.045	0.213	0.554	0.044	0.005	0.068	0.954	0.148	0.030	0.174	0.703	0.162	0.041	0.203	0.459	0.141	0.025	0.159	0.666
27	0.007	0.000	0.008	0.999	0.101	0.015	0.122	0.881	0.247	0.111	0.333	0.111	0.249	0.097	0.312	0.220	0.145	0.034	0.183	0.729	0.122	0.021	0.146	0.828
28	0.024	0.001	0.032	0.990	0.040	0.002	0.047	0.979	0.150	0.038	0.196	0.637	0.129	0.023	0.152	0.781	0.043	0.002	0.049	0.973	0.042	0.002	0.045	0.978
29	0.076	0.009	0.092	0.860	0.091	0.010	0.100	0.835	0.123	0.022	0.150	0.631	0.162	0.045	0.212	0.262	0.201	0.102	0.320	-0.666	0.108	0.015	0.122	0.757
30	0.076	0.009	0.092	0.860	0.091	0.010	0.100	0.835	0.123	0.022	0.150	0.631	0.162	0.045	0.212	0.262	0.201	0.102	0.320	-0.666	0.080	0.009	0.097	0.846

Supplementary Equations:

Supp. Eq (1): $$F_{mass}(t) = \frac{Mass(t)}{Mass_{t=0}}$$

The fractional mass of scaffold remaining at time = t, or $F_{mass}(t)$, where Mass(t) is the mass after in vitro release study and $Mass_{t=0}$ is the initial mass of the scaffold.

Supp. Eq (2):
$$k(x,x') = \sigma_F^2\left(1 + \frac{\sqrt{5}r}{\sigma_L} + \frac{5r^2}{3{\sigma_L}^2}\right)\exp\left(-\frac{\sqrt{5}r}{\sigma_L}\right)$$

Zero Isotropic Matérn 5/2 kernel function (k) for the developed gaussian process regression model describing adjacent observations (x, x') where r is the Euclidean distance between the observations in each feature space, σ_F is the signal standard deviation, and σ_L is the length scale.[3]

Supplementary Files:

File S1 (All Data): All 929 in vitro observations included in model development. Fractional drug released (Observed F(t)) listed in last column corresponding to scaffold # (**Supp. Table 1**), encapsulated drug (Fig. 1B), electrospinning solvent system. Drug-specific properties includes molecular weight (MW, g/mol), partition coefficient (LogP), polar surface area (PSA, Å), and pKa. Scaffold-specific properties includes Ace-DEX % cyclic acetal coverage (%CAC), % drug wt. loading (%Load), fiber diameter (Fd, μm), and time (days). *Excel Sheet 1.*

File S2 (Training): 80% of All Data (Supp. File 1) used for model training. N=744 observations. *Excel Sheet 2.*

File S3 (Testing): 20% of All Data (Supp. File 1) used for model testing. N=185 observations. *Excel Sheet 3.*

File S4 (Performance): Results corresponding to time-matched GPR predictions for All Data (Supp. File 1) including Observed F(t), Predicted F(t), predicted standard deviation (±Stdev), residual error (RE), absolute error (AE), squared error (SE). Shapley values from **Fig. 8A** are also reported for each input parameter. *Excel Sheet 4.*

File S5 (Avg Data): Averages of technical replicates of Observed F(t) in All Data (Supp. File 1) were averaged and indicated as "Avg Observed F(t)" with associated standard deviation (Stdev F(t)). N=276 observations. *Excel Sheet 5.*

File S6 (BSA): GPR simulation results for predicting F(t) for bovine Serum Albumin (BSA)-loaded scaffold (#31). Averages of in vitro technical replicates are reported for the observed F(t) with associated standard deviation (Stdev). Reported Shapley values for each predictor from **Figure 9** are included with each observation. N=8 observations. *Excel Sheet 6.*

File S7: GPR Model Function Code – Code describes how the optimized GPR model is trained and used to make new predictions. Extracted from MATLAB Regression Learner Application. *PDF*.

Supplemental References:

1. Costa, P.; Sousa Lobo, J. M., Modeling and comparison of dissolution profiles. *European Journal of Pharmaceutical Sciences* **2001,** *13* (2), 123-133.
2. David, L. L.; Daniels, A.; Habib, S.; Singh, M., Gold nanoparticles in transferrin-targeted dual-drug delivery in vitro. *Journal of Drug Delivery Science and Technology* **2023,** *90*, 105168.
3. Manzhos, S.; Ihara, M., Degeneration of kernel regression with Matern kernels into low-order polynomial regression in high dimension. *The Journal of Chemical Physics* **2024,** *160* (2).